A.M.A.

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TRENDS IN THE 17-KETOSTEROID EXCRETION OF MALE SEX OFFENDERS JOSEPHINE B. GARST, Ph.D., ET AL.

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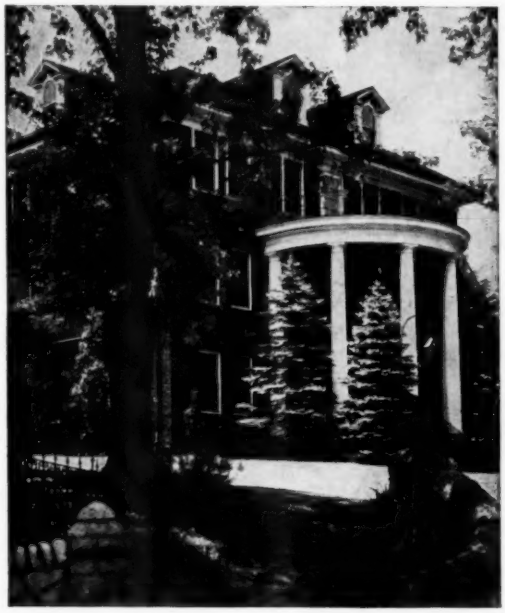

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Neurologic Techniques and Rorschach Test in Detecting Brain Pathology

A Study of Comparative Validities

JEROME FISHER, Ph.D.
and
THOMAS A. GONDA, M.D., San Francisco

This paper presents the results of comparing the validity of the Rorschach test with the validities of individual neurologic procedures in distinguishing between patients with and those without lesions of the central nervous system.

In the process of collecting data on the cross validation of the Rorschach test and its applicability to central nervous system pathology reported in a previous paper,[1] we also obtained data on standard neurologic procedures. The method employed to obtain criterion groups in the cross-validation study was designed so as to provide samples as representative as possible of everyday diagnostic cases in hospital neurology. The method was suggested by Piotrowski [4] about 15 years ago:

> The best control for the cerebral group would seem to be one composed of patients who had been seriously considered to have cerebral lesions and in whom the possibility of cerebral lesions was excluded after a longer period of observation.

Submitted for publication Jan. 28, 1955.

From the Veterans Administration Hospital.
Chief, Clinical Psychology Section, VA Hospital (Dr. Fisher). Assistant Professor of Psychiatry, Stanford University School of Medicine (Dr. Gonda).

METHODS AND MATERIAL

1. Selection of Sample

At the Veterans Administration Hospital, San Francisco, a general medical and surgical hospital, a sample of 118 patients who fulfilled the following requirements was selected: (1) admission to the neurology ward between 1947 and 1953; (2) sufficient hospitalization for a complete neurologic evaluation; (3) status of white, male, veteran; (4) administration of Rorschach examination during hospitalization.

2. Selection of Criterion Groups

The complete hospital records of the 118 patients were presented to two attending neurologists who served as criterion judges.* The medical and neurologic data from which the neurologists made their judgments are summarized in Sections 2 and 3, below. Each judge reviewed the 118 records independently and separated the cases into two groups: those patients in whom, in his opinion, central nervous system pathology was present rostral to the foramen magnum, and those in whom no central nervous system pathology existed rostral to the foramen magnum.† The records include available follow-up clinic notes, as well as special reports, such as autopsy material and letters from other hospitals. All 118 patients had been seen in consultation during hospitalization by one or both of the judges.

* Dr. Henry Newman and Dr. Lewis A. Roberts served as judges in this investigation.

† We acknowledge that the foramen magnum is an arbitrary anatomical dividing line, but, in view of the current limited knowledge of behavioral correlates of the central nervous system, such a point of demarcation is, in our opinion, a reasonable one.

In addition, a 3-point rating scale was provided on which each judge could indicate the degree of certainty with which he categorized each case, viz., "most certain," "certain," "least certain." This kind of rating was provided in order to approximate the manner in which clinical diagnoses, which allow for ambiguities and variations inherent in case material, are made. The ratings obtained from the judges were transposed onto the following scale:

+3: *Most certain* that patient has pathology rostral to foramen magnum

+2: *Certain* that patient has pathology rostral to foramen magnum

+1: *Least certain* that patient has pathology rostral to foramen magnum

—1: *Least certain* that patient has no pathology rostral to foramen magnum

—2: *Certain* that patient has no pathology rostral to foramen magnum

—3: *Most certain* that patient has no pathology rostral to foramen magnum

The numerical values assigned to the judges' ratings of each patient were added algebraically, yielding a combined rating from +6 to —6, thus reflecting the judgment of both neurologists. The distribution of combined ratings was made as follows:

+6 +5 +4 +3 +2 +1	0 —1 —2 —3 —4 —5 —6
Organic criterion group N=84	Nonorganic criterion control group N=34

Thus, the 84 patients who earned combined ratings of +6 to +1 comprise the organic group; the 34 with scores from 0 to —6 are the nonorganic controls.

The use of all 118 cases in the analysis, rather than the less representative design of choosing extremes of the distribution of patients (+6, +5 *vs.* —5, —6), was decided upon because findings on the entire sample allow for better generalization to the population of patients actually encountered in clinical practice, where diagnostic judgments are in reality on a continuum from least to most certain.

How well do the neurologists agree between themselves? When we studied each judge's ratings, we found that they agreed on 86% of the cases with respect to the presence or absence of central nervous system pathology. The coefficient of correlation (ϕ) is 0.64. When we further studied how certain the judges were in their ratings of the presence or absence of central nervous system pathology (i. e., their 6-point ratings, as illustrated above), a higher agreement was obtained, as shown by a ϕ coefficient of 0.76. The discrepancy between the two coefficients results from the fact that the latter correlation takes into account the higher percentage of agreement in the "most certain" categories, in which extreme cases were rated.

The correlation coefficient of 0.76 between the two judges indicates substantial agreement in their classification of the 118 cases but does not indicate how reliable or consistent the combined judgments are. On the grounds that the best criterion of central nervous system pathology is the consensus of a large number of competent neurologists, we can estimate the validity of the combined judgments of two neurologists by computing the estimated correlation between their combined ratings and the "true" combined ratings of numerous comparable neurologists. The estimated "index of reliability" ‡ of our two-judge ratings is 0.93, indicating that considerable confidence may be placed in these combined judgments.

3. Medical Description of Sample

For a better understanding of the characteristics of the sample, a summary and brief analysis of the following data are presented: method of admission to the hospital, nature of medical work-up, age, chief complaint, duration of presenting symptoms, and final diagnosis.

Patients seeking hospitalization are first "screened" by an admitting physician, who decides whether or not hospitalization is indicated. If indicated, or in question, the patients are referred to the admitting physician of the specialty involved, in this instance, neurology. If admitted to the neurology ward, the patients are given a complete medical work-up, including history, physical and neurologic examinations, routine laboratory procedures (complete blood count, blood serology, urinalysis, and chest x-rays), and indicated consultations, as well as special laboratory procedures. In addition, for over six years psychological diagnostic examinations have been requested for a substantial number of neurology patients as part of a continuous "base line" study. These examinations include the taking of a personal and social history, the Rorschach test, the Minnesota Multiphasic Personality Inventory, the Wechsler-Bellevue Intelligence Scale, and other procedures.

Since one of the requirements of the experimental design was that the nonorganic (control) group have as intensive a neurologic investigation as the organic group, a comparison was made of the work-up of the two groups.

Table 1 shows that, with the exception of pneumoencephalography, equivalent procedures were performed on at least 75% of all control cases, and exclusion of the skull x-ray raises the minimum to 88%. It would seem, therefore, that this requirement has been met.

‡ Reference 2, p. 413.

TABLE 1.—*Per Cent of Cases in Criterion Groups on Which Neurologic Procedures Were Performed*

	Organic	Nonorganic
Complete history	100	100
Physical and neurologic examination	100	100
Neurologic consultation	100	100
Routine laboratory procedures	100	100
Electroencephalogram	98	94
Lumbar punctures	93	88
Skull x-rays	93	77
Pneumoencephalogram (ventriculogram and/or arteriogram)	63	21

As to age, for the organic group the range is 21-60, with a mean age of 38 years. For the control, nonorganic, group the range is 22-57, with a mean age of 33 years. The difference of five years between the groups is not significant statistically. Also, no significant differences were found between the two criterion groups in I. Q., education, or socioeconomic status.

The chief complaints § are listed in Table 2. Disturbances of consciousness, characterizing half the sample, were expressed in terms of various "spells" and "attacks," including "black-outs," "convulsions," "cut-off" spells, "dizzy" spells, "falling-out" spells, epileptic attacks, fainting, seizures, and "sleepy" spells. Motor symptoms (22%) included complaints of incoordination, involuntary movements, palsy, paralysis, shaking, spasms, tightening of muscles, trembling, and weakness. Headaches (16%) as the primary complaint were variously described. Sensory symptoms (9%) included complaints of numbness, pain, tingling, and visual difficulty. Where complaints about psychological functioning were primary (4%), they included confused wandering, mental deterioration, nervousness, visions, and voices. It was also found that in over 15% of the sample (organic, 16%, and nonorganic, 15%) symptoms secondary to the chief complaint included such psychological disturbances as amnesia, behavioral change, déjà vu, fugue, insomnia, memory change, nervous spells, and psychosis. A comparison of the chief complaints of the organic and nonorganic groups is also shown in Table 2. Worthy of special comment is that headache (8%) and sensory symptoms (2%) were uncommon primary complaints in the organic group, but constituted significantly the chief complaint in over 60% (26% and 35%, respectively) of the nonorganic group. Of note, too, is that a complaint of disturbance of consciousness points significantly toward the organic group.

§ Where there were complaints of more than one symptom, the primary symptom which brought the patient to seek hospitalization was used for tabulation.

TABLE 2.—*Per Cent of Chief Complaints Presented by Cases in the Criterion Groups*

	Organic	Non-organic	Total
Disturbance of consciousness	60	18	48
Motor symptoms	24	18	22
Headache	8	35	16
Sensory symptoms	2	26	9
"Psychiatric" symptoms	5	3	4
Other symptoms	1	0	1

Table 3 lists the duration of the primary symptoms. Of the 118 cases, 53% had their symptoms for more than three years; 44%, less than three years, the duration of illness not being established in 3%. Table 3 also shows a comparison of the duration of the chief complaint in the organic and in the nonorganic group. The data reveal that when these symptoms are of more than three years' duration, the case is reliably likely to fall into the nonorganic category. Also, the trend in the data indicates that when these symptoms are of less than one month's duration the case is likely, but not reliably so, to fall into the organic category.

TABLE 3.—*Per Cent of Cases According to Duration of Primary Symptoms*

	Organic	Non-organic	Total
Less than 1 mo.	21	9	18
1 mo. to 6 mo.	11	9	10
6 mo. to 3 yr.	18	12	16
Over 3 yr.	48	67	53
Not known	2	3	3

As to the final diagnoses given in Table 4, these were frequently multiple, and, of course, included diseases other than those of the nervous system and the psychobiologic unit. However, for purposes of this study, only those diagnoses referable to the above categories were tabulated and analyzed. For purposes of uniformity and convenience, the diagnoses were grouped in conformance with the "Standard Nomenclature of Diseases," [5] under the following six major headings.

NSG: Diseases of the nervous system generally
DB: Diseases of the brain
SCN: Diseases of the spinal cord, nerve roots, and peripheral nerves
CD: Convulsive disorders (nonsymptomatic)
PBU: Diseases of the psychobiologic unit, i. e., psychiatric diagnosis only
NNP: No neurologic or psychiatric diagnosis

Table 4 shows a comparison of the final diagnosis in the organic and in the nonorganic group. Only 16% of the sample had a psychiatric diagnosis alone. We did find, however, that 45% of the sample

TABLE 4.—*Per Cent of Cases with Final Primary Diagnoses*

	Organic	Non-organic	Total
NSG	14	0	10
DB	58	23.5	48
SCN	4	23.5	9
CD	18	0	13
PBU	5	41	16
NNP	1	12	4

(organic, 23%, and nonorganic, 68%) also carried an additional psychiatric diagnosis. We discovered also that eight cases diagnosed as having a disease of the brain were classified as nonorganic by the judges. The significance of this discrepancy is not known, though it reflects an independence of the judges, who most assuredly took into account more than the final diagnosis in separating the cases.

4. Procedures and Methods of Analysis

With regard to the five different techniques compared here, the following criteria for dividing the cases into organic and nonorganic were applied for purposes of statistical analysis:

(*a*) *Complete Neurologic Examinations.*—The examinations were performed on each of the 118 patients, most of them having been examined on several occasions by different staff members. If any of the observers reported any neurologic sign, even a single equivocal finding, the examination was called "positive"; it was called negative only in the complete absence of reported abnormality.‖

(*b*) *Electroencephalographic Study.*—One or more EEG's was performed on 97% of the patients (114). Focal abnormalities ("positives") are those which were found to be focal in the routine waking method, with use of four different combinations of electrodes, each for two to two and a half minutes, and three minutes of activation by hyperventilation. Focal records obtained by other types of activation were categorized under "other abnormalities," as were records showing lateralization alone, diffuse abnormalities, and borderline or equivocal findings. Only when all of the tracings taken were read as normal was the case placed in the group of "negatives."

(*c*) *Lumbar Puncture.*—These were performed on 92% of the 118 patients. If a single finding—manometric, gross, microscopic, biochemical, or serologic—deviated from the range of normal ¶ for this hospital, the result was called "positive." Only when all findings were within normal limits was the lumbar puncture called "negative."

(*d*) *Skull X-Rays.*—These were taken in 88%, and the pneumoencephalograms, ventriculograms, and arteriograms were done on 51%, of the 118 patients. Equally rigid criteria of negativity were used. Any findings of abnormality, even if nonincidental to the patient's illness, was called "positive."

(*e*) *Rorschach Test.*—Each of the 118 cases had been administered the Rorschach test as part of a larger psychological examination during hospitalization by one or another of 32 clinical psychologists. These workers varied considerably in experience, competence, and skill. It is assumed that such diverse degrees of competence assures representativeness of the results because it approximates the general situation in clinical practice today. All Rorschach protocols were reviewed and the scoring checked by one of us prior to the categorization of the cases according to the criterion. The "organic signs," as presented by Piotrowski,[3] were tabulated for each protocol, and the cut-off score of 5 recommended by Piotrowski was then used to categorize each case as "positive" or "negative."

RESULTS

Table 5 presents the fourfold frequency tables from which association measures between the criterion and the various predictive tools are derived, and other measures computed. In each Table, the entry in the upper left-hand cell indicates the number of cases

‖ Several legitimate objections may be presented to this arbitrary method of analyzing positive and negative results of the neurologic examinations. For example, a positive sign on the neurologic examination may or may not be related to central nervous system pathology rostral to the foramen magnum. Also, it is recognized that these signs have varying degrees of reliability, and that wide differences are shown among the examiners themselves, as well as between examinations by one examiner.

Perhaps the foramen magnum as an anatomical cut-off line is not valid for studying the neurologic examination in the way we have. Yet, the question still remains: Which division? Spinal cord and brain *vs.* peripheral nerves? Even with this division there may be some positive neurologic signs whose interpretation cannot differentiate any more reliably than the division used in this study.

¶ Manometric: Under 200 mm. of water for recumbent position.

Gross: Fluid must be clear and colorless.

Microscopic: Less than 6 white blood cells per cubic millimeter.

Biochemical: Protein less than 40 mg/100 cc.

Serologic: Negative reaction.

Prof. Robert C. Tryon, of the University of California, assisted in the analysis of the data.

TABLE 5.—*Frequency Tables Showing Associations Between Criterion and Various Predictive Tools*

Tool		Criterion * NO	Criterion * O		ϕ Coefficient	S. E.	*P*
EEG	POS †	12	59	71	0.324	0.093	0.01
	NEG	20	23	43			
		32	82	114			
		NO	O				
Pneumoencephalogram, etc....	POS	2	26	28	0.134	0.129	Insignificant
	NEG	5	27	32			
		7	53	60			
		NO	O				
Skull x-rays	POS	2	15	17	0.136	0.098	Insignificant
	NEG	24	63	87			
		26	78	104			
		NO	O				
Neurologic examination	POS	14	60	74	0.284	0.092	0.01
	NEG	20	24	44			
		34	84	118			
		NO	O				
Lumbar puncture	POS	1	22	23	0.274	0.096	0.01
	NEG	29	56	85			
		30	78	108			
		NO	O				
Rorschach (Piotrowski)	POS	2	32	34	0.322	0.092	0.001
	NEG	32	52	84			
		34	84	118			

* O indicates organic; NO, nonorganic.
† POS indicates positive; NEG, negative.

which were identified by the diagnostic tool as organic, but which were nonorganic according to the criterion; the entry in the upper right-hand cell is the number of cases which were identified as organic by the diagnostic technique and also by the criterion. The lower left-hand cell contains the number of cases which the diagnostic technique and the criterion identified as a nonorganic, and the lower right-hand cell, the number of cases found to be nonorganic by the technique and organic by the criterion.

To the right of each diagram is given the ϕ correlation coefficient and its standard error. These correlation coefficients measure the degree of association (validity coefficient) between the diagnostic techniques and the dichotomized criterion judgments of brain pathology. With the exception of the coefficients obtained from pneumoencephalograms, etc., and the skull x-rays, all are statistically significant, indicating that the EEG's, the neurologic examination, the lumbar puncture, and the Rorschach test detect patients with brain pathology better than chance. The low magnitude of these ϕ coefficients does not entirely do justice to the specific tool-criterion relationships. For this reason, the same data were summarized differently, and these are presented in Table 6.

TABLE 6.—*Screening Efficiency of Various Predictive Tools**

Tool	(1) Call Rate	(2) False Positives	(3) False Negatives	(4) Tool Accuracy
Neurologic examination	63%	41%	29%	81%
EEG	62	38	28	83
Pneumoencephalogram, etc.	46	29	51	93
Rorschach (Piotrowski)	29	6	62	94
Lumbar puncture	21	3	72	95
Skull x-rays	16	8	81	88

* Column (1): All cases called organic by the tool divided by the total number of cases to which the tool was applied.

Column (2): Per cent of cases which the tool called organic but which the criterion called nonorganic.

Column (3): Per cent of cases which the tool called nonorganic but which the criterion called organic.

Column (4): All cases the tool called organic correctly divided by the total number of cases the tool called organic.

The "call rate" of each diagnostic tool is shown in Column (1), i. e., the per cent called positive by the tool. This per cent is an estimate of how often in a similar population the individual tool may be expected to yield a positive finding. It is readily apparent that the EEG (62%) and the neurologic

examination (63%) clearly call more cases of the total sample organic than the other tools do.

The next highest "call rate" is the pneumoencephalographic procedures, which are found to call 46% of all cases organic. It is to be noted in Table 5 that these procedures were applied selectively, i. e., where indicated by the physician, and to only 60 cases of the entire sample. The presence of a certain degree of bias in the way these cases were chosen for observation by this tool strongly suggests that the estimated "call rate" (46%) of the pneumoencephalographic procedures is too high.

The Rorschach test, lumbar puncture, and skull x-rays follow, with call per cents of 29, 21, and 16, respectively, indicating that these diagnostic procedures have distinct limitations for purposes of preliminary screening.

An efficient diagnostic procedure, however, should not screen into the organic category too many nonorganic cases (false positives) in the process of identifying organic cases. Hence we turn our attention to "accuracy" of identification of organic cases, as defined by the criterion. For this purpose, the data have been analyzed in terms of "false positives," "false negatives," and "tool accuracy."

Column (2) shows the per cent of false positives for each tool. It is the proportion of the criterion nonorganic cases called organic (positive) by the tool. (See Table 5; for example, for the EEG, it is the proportion 12/32, or 38%.) It is clear that, although the neurologic examination and the EEG in their "call rates" call more organic cases than do the Rorschach test, lumbar puncture, and skull x-rays, they are inclined to misidentify some 40% of nonorganic cases as organic. In contrast, the Rorschach test, lumbar puncture, and skull x-rays tend to be conservative in calling organic cases, but they rarely err in false positives (6%, 3%, and 8%, respectively).

Column (3) presents the per cents of false negatives, i. e., per cents of cases which the criterion calls organic but which the tool calls nonorganic. (See Table V; for example, for the EEG, it is the proportion of 23/82, or 28%.) The results indicate that the EEG and the neurologic examination give false-negative findings in approximately 30% of the organic cases, while the other tools exceed 50% in false-negative findings.

Perhaps of greater significance to the clinician is the validity of a given diagnostic procedure when it yields a positive finding. It is apparent from Column (4), therefore, that the Rorschach test and lumbar puncture are valid 94% and 95% of the time, respectively, when they call a case organic. The neurologic examination, however, agrees with the criterion 81% of the time when it gives a positive finding. The pneumoencephalographic procedures show an accuracy of 93%, but, again, its selective use in only 60 of the 118 cases makes this figure suspect of probably being larger than would have been found if used on as many patients as the other tools.

COMMENT

Although various interpretations may be made of the results, it is apparent that while the EEG and the neurologic examination employed in daily neurologic practice have a high call rate, their over-all validity suffers in that they falsely call 40% of the nonorganic cases organic. On the other hand, the Rorschach test, lumbar puncture, and skull x-rays are less sensitive as calling procedures, but their errors are reflected in the higher percentages of "false negatives," perhaps not so serious an error in clinical practice. However, the number of false positives for these techniques is remarkably low, being, of course, reflected in their relatively high degree of accuracy (94%, 95%, and 88%, respectively) when they yield a positive (organic) finding.

An important point should be emphasized: Because the criterion was based in part on the neurologic findings, the validity obtained for the neurologic techniques is probably inflated. Since the Rorschach test did not enter into the establishment of the criterion, the findings show that as an isolated procedure it is superior to the best of the individual

neurologic techniques in diagnosing the presence of brain disease. The results of this study, therefore, warrant the inclusion of the Rorschach test among the diagnostic, consultative procedures of the clinical neurologist.

There are some interesting applied and theoretical implications in this study. Clinical neurologists and other medical specialists tend to disregard a negative finding in an individual case if, in their opinion, this finding opposes the patient's history, presenting complaints, symptoms, and other diagnostic data. A positive finding, however, is regarded with considerable respect provided the diagnostic technique is accurate in 80% of the cases at least. In the instance of a negative finding, the physician usually functions with a realistic tolerance for error and clinical relativism. We can understand this from our data, for we observed that there are relatively large numbers of false negatives in five currently used standard neurologic procedures. In the case of a positive call by the Rorschach test, i. e., when five or more Piotrowski signs are present, the Rorschach test demonstrates a 94% accuracy; when there are four or less signs, the finding is inconclusive because of the large number of false negatives.

Several questions occur to us. 1. Why do the standard neurologic tools yield so many false negatives? 2. Why do neurologists persist in using these tools despite their clinical appreciation of these errors?

From the results of our study, we may assume that the errors in the diagnostic tools themselves play a part in the yield of false negatives. We suspect, however, that there may be biological factors in operation which our diagnostic techniques cannot take into account at this stage of our knowledge. Our hypothesis is that when pathology is present in the adaptive human organism, homeostatic mechanisms are involved actively and continuously to compensate in ways which seek to restore the organism to its former state. This on-going process may account for "normal" responses (false negatives) to our tools in spite of the presence of pathology. Our techniques seemed to have been devised so as to assess pathology in status, i. e., when adaptiveness has been curtailed beyond a certain point. Perhaps, in addition, we need to devise other diagnostic procedures which could "see" through the camouflage of compensatory mechanisms by which the adaptive organism constantly strives toward reestablishment of its natural state and ultimate continuation of its survival.

SUMMARY AND CONCLUSIONS

This study compares the validities of standard neurologic techniques with the validity of a Rorschach sign method (Piotrowski) in the diagnosis of brain disease.

The sample consists of 118 patients, all of whom were admitted to the neurology ward of a Veterans Hospital with various complaints and symptoms referable to the nervous system. All patients received thorough neurologic work-ups, including electroencephalograms, skull x-rays, and lumbar punctures. In addition, a Rorschach test had been administered to each patient as part of a psychological examination. Diagnostic procedures, such as pneumoencephalography, were performed as indicated.

The criterion groups were derived as follows: Two attending neurologists studied independently the completed hospital charts of the 118 patients. In addition, all cases had been examined in consultation by one or the other of them. They judged 84 patients as having pathology above the foramen magnum and the remaining 34 patients as presumably having no such pathology. The groups were found to be comparable in age, intelligence, education, and socioeconomic status. An index of reliability of 0.93 indicated a high agreement between the two neurologists and the pooled ratings of many comparable neurologists.

This investigation differs from previous research on brain pathology in that there was obtained (1) greater representativeness to actual practice through the selection of cases from a general hospital neurology ward, yielding a continuum of cases from extreme through borderline to no brain pathology; (2) differentiation between the group with

brain pathology and the control group on the basis of intensive neurologic work-up rather than of psychiatric diagnosis, and (3) a measure of the reliability of the criterion.

The validity coefficients (ϕ) show that of the six diagnostic procedures studied, the Rorschach method discriminates very reliably between the organic and the nonorganic groups. The EEG, the neurologic examination, and the lumbar puncture also differentiate significantly between the groups. The skull x-rays and pneumoencephalograms, however, fail to demonstrate stable differences.

In addition, the findings indicate that high call rates of brain damage are characteristic of the neurologic examination (63%) and the EEG (62%); they err mainly in the direction of calling almost 40% of nonorganic cases organic. On the other hand, the Rorschach method, lumbar puncture, and skull x-rays call fewer organic cases (29%, 21%, and 16%, respectively), and their errors are reflected in higher percentages of "false negatives." However, the number of "false positives" for these techniques is remarkably low. They reveal a high tool accuracy (94%, 95%, and 88%, respectively) when they call a case organic.

Because the criterion was based in part upon the neurologic techniques, and not upon the Rorschach method, the findings show that as an isolated procedure, the Rorschach is superior to the best of the individual neurologic techniques in detecting the presence of brain disease, and therefore warrants inclusion among the diagnostic consultative procedures of the clinical neurologist.

An hypothesis is stated to explain why our currently used diagnostic techniques give so many false negatives in the presence of actual disease.

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Trends in the 17-Ketosteroid Excretion of Male Sex Offenders

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Available evidence indicates that three determinants underlie the psychosexual behavior of man, viz., the social environment, the personality structure, and the neuroendocrine system (particularly the hypothalamo-hypophysial-gonadal complex). There is reason to believe, moreover, that the functional status of the neuroendocrine system is influenced to a considerable degree by sociocultural and other environmental determinants.[1] However, functional variations in the neuroendocrine system per se are not without effect on the pattern of sexual behavior; clinically significant psychic disturbances occur in association with male hypogonadism[2] and the hyperadrenocortical states, and the administration of androgenic substances restores the libido and the capacity for coitus in cases of gonadal deficiency.[3]

In view of the foregoing, we investigated the steroid excretion of male sex offenders as a part of a study of the pathogenesis of this condition. At the time this investigation was undertaken, it was most feasible from the standpoint of methodology and certain biochemical considerations to study only the excretion of the 17-ketosteroids (17-KS). Accordingly, determinations were made of the 12-hour and 24-hour excretion levels, and of the ratio of alpha- to beta-3-hydroxy-17-ketosteroids. Since urinary 17-KS are metabolites of both testosterone and the adrenocortical steroids (both 11-oxy- and 11-desoxy types),[4] the 24-hour excretion levels of these steroids constitute an index of both gonadal and adrenocortical activity. Furthermore, the ratio of 17-KS excretion during the day to that at night (D:N ratio) is believed to reflect the response of the adrenal cortex to stress,* and there is some evidence to the effect that the excretion of dehydroepiandrosterone (a 3β-hydroxy-17-ketosteroid) is reduced to zero in persons with depression.†

MATERIALS AND METHODS

Two groups of male subjects were used for this study: a control group of 15 medical students and research workers, and a group of 49 sex offenders.‡ The latter were confined at the Metropolitan State Hospital for a period of observation and treatment under the California Sex Psychopath Act. Only those persons showing no clinically demonstrable evidence of organic disease were used for this study. Blood white cell counts and sedimentation rates were carried out immediately prior to the collection of the urine samples in the case of the sex offenders in order to rule out infectious states. No overt homosexuals or psychotics were included.

One to three pairs of consecutive 12-hour urine specimens were collected on each subject. The first specimen of urine voided after arising was dis-

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‡ Offenses leading to their conviction include indecent exposure, child molestation, rape, and homosexual contact with minors.

carded. The daytime collection was begun immediately thereafter and continued for 12 hours. Collection of the night-time specimen was then begun and continued through the first specimen voided after arising. Care was taken to keep these specimens refrigerated and to protect them from light, since it is known that in the presence of riboflavin light has a destructive action on certain steroids.[8] The 17-KS determinations were made by a method of hydrolysis and extraction perfected in this laboratory.§ In this extraction process, 6 N sulfuric acid is used in place of concentrated hydrochloric acid for the hydrolysis of the conjugates to obviate the conversion of dehydroepiandrosterone to 3-chloro-Δ^5-androstenone-17. The assay method used is a modification § of the Callow absolute alcohol technique for the Zimmermann reaction.

The color test of Allen and associates [9] was employed for the determination of the ratio of α- to β-3-hydroxy-17-ketosteroids. Even though this test is not highly specific for androsterone and dehydroepiandrosterone, the results are as valid as those obtained by the currently accepted method of digitonin separation. In view of this, the decision to use the Allen color test hinged on the fact that of the two it is the more easily performed. The Coleman Junior spectrophotometer was used to determine the optical density of the samples instead of the Beckman spectrophotometer because the reaction of the samples with the ethanol-sulfuric acid reagent could then be carried out in the spectrophotometer tubes. In this instrument, pure samples of androsterone, etiocholanolone, and dehydroepiandrosterone gave spectral curves with peaks at 470, 480 and 580 mμ, respectively. For androsterone this is a secondary peak, the maximum being at a wave length less than 400 mμ. The density values at wave lengths of 470 and 580 mμ resulted in the greatest difference between the spectral curves for androsterone and those for dehydroepiandrosterone under these experimental conditions. These density values probably represent principally the three aforementioned steroids, since other steroids (which might interfere) either are not present in normal urine or do not contribute appreciably to the density values.

§ Garst, J. B., and Friedgood, H. B.: Unpublished data.

RESULTS

17-Ketosteroid Excretion of Sex Offenders as Compared with That of the Controls

When the 24-hour excretion values for the three groups of subjects were pooled and divided into two groups according to age, it was found that there was a statistically significant difference in the values for subjects 35 years or younger, as compared with those for subjects more than 35 years of age (Table 1). This is in agreement with the findings of others.|| Analysis of the 17-KS D : N ratios for the same age groups showed no significant difference with age (Table 1). A comparison of the data for the sex offenders with those for the controls is shown in Table 2. Even though the number of control subjects is small, the mean values found for the two age groups appear to be fairly representative. Ceresa and Rubino [10] obtained an average daily level of 11.41 mg. for men 20 to 30 years of age and 9.18 mg. for those 31 to 45 years of age, and Hamilton [12] has reported an average value of 12.5 mg. for men between 20 and 39 years and 9.7 mg. for men between 40 and 59 years. It will be noted that although no significant difference was found in the 24-hour excretion values for the sex offenders of either age group as compared with the controls, the median values for the sex offenders are from 15% to 25% lower than those for the controls. The difference in the 17-KS D : N ratios for the sex offenders as compared

|| References 10 and 11.

Table 1.—*Variation of 17-Ketosteroid Excretion with Age*

Age, Yr.	No. of Persons	No. of Samples	Average Value	Median	Median Values, χ^2	Probability Level
			Mg./24 Hr.	Mg./24 Hr.		
24-hour excretion						
17-35	42	95	10.98	10.39	6.82	0.009 *
36-58	22	42	8.06	7.10		
			D:N Ratio	D:N Ratio		
Day-to-night excretion						
17-35	28	63	1.48	1.22	0.237	0.580
36-58	20	37	1.34	1.18		

* Difference between groups may be expected to be due to chance 9 and 580 times, respectively, in 1,000 samples.

TABLE 2.—*Comparison of 17-Ketosteroid Excretion Values of Sex Offenders with Control Values*

	No. of Persons	No. of Samples	Mean Values, Standard Deviation (Mg./24 Hr.)	Median Values: Mg./24 Hr.	Median Values: Mood Test *P* Level	Second Item of Pair Over First, %
24-Hour Excretion						
17-35 yr.						
Controls	13	29	12.28 ± 4.97	12.11	0.247 *	85
Sex offenders	29	66	10.39 ± 4.03	10.34		
36-58 yr.						
Controls	2	7	9.23 ± 1.73	9.23	0.217	75
Sex offenders	20	35	7.98 ± 3.22	6.96		
Day-to-Night Excretion						
			Ratios	Ratios		
All ages						
Controls	7	19	1.05 ± 0.15	1.06	0.057	123
Sex offenders	41	81	1.48 ± 0.86	1.30		

* Difference between groups may be expected to be due to chance 247 times in 1000 samples. Similar interpretation applies to other *P* values.

with those for the controls is of borderline significance, the median values for the sex offenders being higher than those for the controls.

RELATIONSHIP OF AGGRESSIVENESS OF SEX OFFENDERS TO 17-KETOSTEROID EXCRETION

Since certain of the sex offenders showed aggressiveness toward their victims whereas others did not, the data were examined from this standpoint. Table 3 shows that by the Mood Test there is no significant difference in the median 24-hour excretion values for either the aggressive or the nonaggressive group as compared with the control values. The median values for the sex offenders, however, are from 15% to 30% lower than the medians for the controls. When the sex offenders are similarly grouped, the 17-KS D:N ratio discloses a significant difference for the nonaggressive offenders, but not for the aggressive offenders, as compared with the controls. In both these cases, however, the median value for the sex offenders is higher than the median value for the controls.

TABLE 3.—*17-Ketosteroid Excretion Data of Aggressive and Nonaggressive Sex Offenders Compared with Controls*

	No. of Persons	No. of Samples	Mean Values, Standard Deviation (Mg./24 Hr.)	Median Values: Mg./24 Hr.	Median Values: Mood Test *P* Level	Second Item of Pair Over First, %
24-Hour Excretion						
17-35 yr.						
Controls	13	29	12.28 ± 4.97	12.11		
* A-Sex offenders	8	13	9.72 ± 3.31	9.91	0.272 †	82
Controls	13	29	12.28 ± 4.97	12.11		
NA-Sex offenders	21	53	10.65 ± 4.25	10.34	0.259	85
36-58 yr.						
Controls	2	7	9.23 ± 1.73	9.23		
A-Sex offenders	7	12	7.53 ± 2.44	7.84	0.556	85
Controls	2	7	9.23 ± 1.73	9.23		
NA-Sex offenders	14	23	8.21 ± 3.37	6.56	0.233	71
Day-to-Night Excretion						
			Ratios	Ratios		
All ages						
Controls	7	19	1.05 ± 0.15	1.06		
A-Sex offenders	14	22	1.37 ± 0.45	1.20	0.179	113
Controls	7	19	1.05 ± 0.15	1.06		
NA-Sex offenders	28	60	1.53 ± 1.00	1.35	0.005	127

* A indicates aggressive offenders and NA, nonaggressive offenders.

† Difference between groups may be expected to be due to chance 272 times in 1,000 samples. Similar interpretation applies to other *P* values.

TABLE 2.—*Comparison of 17-Ketosteroid Excretion Values of Sex Offenders with Control Values*

	No. of Persons	No. of Samples	Mean Values, Standard Deviation (Mg./24 Hr.)	Median Values: Mg./24 Hr.	Median Values: Mood Test *P* Level	Second Item of Pair Over First, %
24-Hour Excretion						
17-35 yr.						
Controls	13	29	12.28 ± 4.97	12.11	0.247 *	85
Sex offenders	29	66	10.39 ± 4.63	10.34		
36-58 yr.						
Controls	2	7	9.23 ± 1.73	9.23	0.217	75
Sex offenders	20	35	7.98 ± 3.22	6.96		
Day-to-Night Excretion						
			Ratios	Ratios		
All ages						
Controls	7	19	1.05 ± 0.15	1.06	0.057	123
Sex offenders	41	81	1.48 ± 0.86	1.30		

* Difference between groups may be expected to be due to chance 247 times in 1000 samples. Similar interpretation applies to other *P* values.

with those for the controls is of borderline significance, the median values for the sex offenders being higher than those for the controls.

RELATIONSHIP OF AGGRESSIVENESS OF SEX OFFENDERS TO 17-KETOSTEROID EXCRETION

Since certain of the sex offenders showed aggressiveness toward their victims whereas others did not, the data were examined from this standpoint. Table 3 shows that by the Mood Test there is no significant difference in the median 24-hour excretion values for either the aggressive or the nonaggressive group as compared with the control values. The median values for the sex offenders, however, are from 15% to 30% lower than the medians for the controls. When the sex offenders are similarly grouped, the 17-KS D:N ratio discloses a significant difference for the nonaggressive offenders, but not for the aggressive offenders, as compared with the controls. In both these cases, however, the median value for the sex offenders is higher than the median value for the controls.

TABLE 3.—*17-Ketosteroid Excretion Data of Aggressive and Nonaggressive Sex Offenders Compared with Controls*

	No. of Persons	No. of Samples	Mean Values, Standard Deviation (Mg./24 Hr.)	Median Values: Mg./24 Hr.	Median Values: Mood Test *P* Level	Second Item of Pair Over First, %
24-Hour Excretion						
17-35 yr.						
Controls	13	29	12.28 ± 4.97	12.11		
* A-Sex offenders	8	13	9.72 ± 3.31	9.91	0.272 †	82
Controls	13	29	12.28 ± 4.97	12.11		
NA-Sex offenders	21	53	10.65 ± 4.25	10.34	0.250	85
36-58 yr.						
Controls	2	7	9.23 ± 1.73	9.23		
A-Sex offenders	7	12	7.53 ± 2.44	7.84	0.556	85
Controls	2	7	9.23 ± 1.73	9.23		
NA-Sex offenders	14	23	8.21 ± 3.37	6.56	0.233	71
Day-to-Night Excretion						
			Ratios	Ratios		
All ages						
Controls	7	19	1.05 ± 0.15	1.06		
A-Sex offenders	14	22	1.37 ± 0.45	1.20	0.179	113
Controls	7	19	1.05 ± 0.15	1.06		
NA-Sex offenders	28	60	1.53 ± 1.00	1.35	0.005	127

* A indicates aggressive offenders and NA, nonaggressive offenders.

† Difference between groups may be expected to be due to chance 272 times in 1,000 samples. Similar interpretation applies to other *P* values.

TABLE 5.—*Ratio of α- to β-3-Hydroxy-17-Ketosteroids in Urinary Neutral Steroid Residues*

	No. of Persons	No. of Samples	Median *	Median Values, χ^2	Probability Level
17-35-yr. groups					
Controls	12	51	1.65	0.104	0.800 †
Sex offenders	29	122	1.66		
36-58-yr. groups					
Controls	2	12	1.80	0 ‡	0
Sex offenders	20	64	1.92		
Pooled groups					
17-35 yr.	41	173	1.66	6.48	0.011
36-58 yr.	22	76	1.92		

* Ratio of readings at 470/580mμ, the peak maximum shown by androsterone and dehydroepiandrosterone under the conditions used for this work.
† Difference between groups may be due to chance 800 and 11 times, respectively, in 1,000 samples.
‡ The value of N in this group is too small for the determination of χ^2.

(Table 3). However, the difference between the median values of 17-KS D:N ratios for the controls and for the sex offenders as a whole is of borderline significance. Although the rest of our data is not statistically significant, there are obvious trends which appear to be worthy of further investigation.

Twenty-Four-Hour Excretion Rate.—It will be noted that the 24-hour excretion rate of 17-KS is lower for the sex offenders, in general, than for the controls. Since the level of excretion of 17-KS is dependent both on the gonads and on the adrenal cortex in men, it is impossible to say whether one gland or both are responsible for this decrease. Furthermore, the indications are that preparations of corticotropin currently in use not only stimulate the adrenal cortex to produce adrenal cortex hormones per se and sex hormones, but also stimulate the gonads to produce cortical hormones.[13] A similar biglandular type of action has been noted for the gonadotropic hormones in relation to the adrenal cortex and the gonads.[13] According to Zuckerman,[13] the central feature of the adrenogenital relationship is the community of control and community of response. This concept differs fundamentally from what is currently believed concerning other endocrine relationships. Should Zuckerman's views prove valid, it is clear that the functional activity of both the adrenal cortex and the gonads would be depressed through one or the other, or both, of these types of trophic hormones. The clinical implications of the latter are highly suggestive from what is now known about the depressant effects of malnutrition[14] and unconscious emotional conflicts[1] on adenohypophysial functions.

Day-to-Night Ratios.—The trend to higher-than-normal 17-KS D:N ratios shown by the sex offenders appears to indicate a greater-than-normal degree of reactivity of the adrenal cortex to the stresses of daily living. It will be noted, however, that the absolute level of excretion, as shown by the 24-hour values, is lower than normal.

SUMMARY

The excretion of 17-ketosteroids has been investigated in sex offenders and compared with that of normal controls. The statistically significant findings are twofold, viz., the difference between the 17-ketosteroid day-to-night ratios for the nonaggressive sex offenders and for the controls, and between the 17-ketosteroid day-to-night ratios for the sex offenders as a whole and for the controls. Although lacking in statistical significance, other data revealed trends which appear to be worthy of further study; e. g., as compared with the controls, the average 24-hour 17-ketosteroid excretion is lower, and the average day-to-night ratio of 17-ketosteroid excretion is higher, for the sex offenders.

Dr. Harry B. Friedgood assisted in the initial planning of the work, and Mrs. Jessamine Hilliard and Mr. Robert Liechti supervised the collection of the urine specimens.

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Arterenol (Norepinephrine) and Vascular Headache of the Migraine Type

Studies on Headache

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and
HAROLD G. WOLFF, M.D., New York

It has been appreciated for some time that agents that effectively induce cranial vasoconstriction also reduce the intensity of, or eliminate, vascular headache of the migraine type. The potency of arterenol (norepinephrine) as a vasoconstrictor suggested that it might affect the intensity and duration of the pain and further elucidate the mechanism of vascular headache.*

METHOD

Arterenol in a dilution of 4 cc. of a 0.2% solution in a liter of 5% dextrose in water was administered intravenously at an average rate of 1 drop per second, or sufficient to raise the systolic blood pressure 10 to 40 mm. Hg. With the patient supine, blood pressure and pulse were determined at intervals of 1 to 2 minutes initially and thereafter every 10 to 15 minutes. Pulse wave tracings of the involved cranial arteries were made using the apparatus described in a previous communication.[4] Deep-pain thresholds of the scalp were assayed by means of the Hardy deep-pain dolorimeter (Fig. 1).[5] When possible, the diameter of relevant dilated cranial vessels was measured directly at intervals during arterenol infusion, and observations were made of the accompanying phenomena, such as edema, conjunctival injection, and rhinorrhea. The patient's reports of the effects of the arterenol on the intensity of the headache were recorded.

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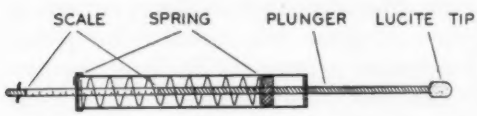


Figure 1

RESULTS

Series 1.—Arternol, in the manner described above, was administered on 116 occasions to 35 patients with vascular headache of the migraine type. On 93 of these occasions the headache began to diminish in 10 to 60 minutes and was either eliminated or much reduced in intensity in an average time of 82 minutes, the range being from 20 to 160 minutes. In general, the more intense the headache the longer the time required for its elimination. Mild headaches have been terminated in 20 minutes, severe headaches persisting for as long as 160 minutes after beginning arterenol infusion. In four instances of status hemicranicus this agent was without significant effect.

Ophthalmic involvement, in the form of conjunctival injection, tearing, blurred vision, or photophobia, was present in 36 of the 116 headache attacks. These phenomena were eliminated in every instance. Consistently they were terminated more rapidly than other headache phenomena. Ten to 15 minutes of infusion sufficed to relieve them. Nasal mucosal injection and/or rhinorrhea was present in eight headache attacks and also was relieved in every instance. Usually 30 to 45 minutes of infusion was required to terminate the nasal symptoms. Edema of the scalp was a frequent finding. The degree of edema could be readily estimated by the depth of depression made by applying a standard pressure with the Hardy

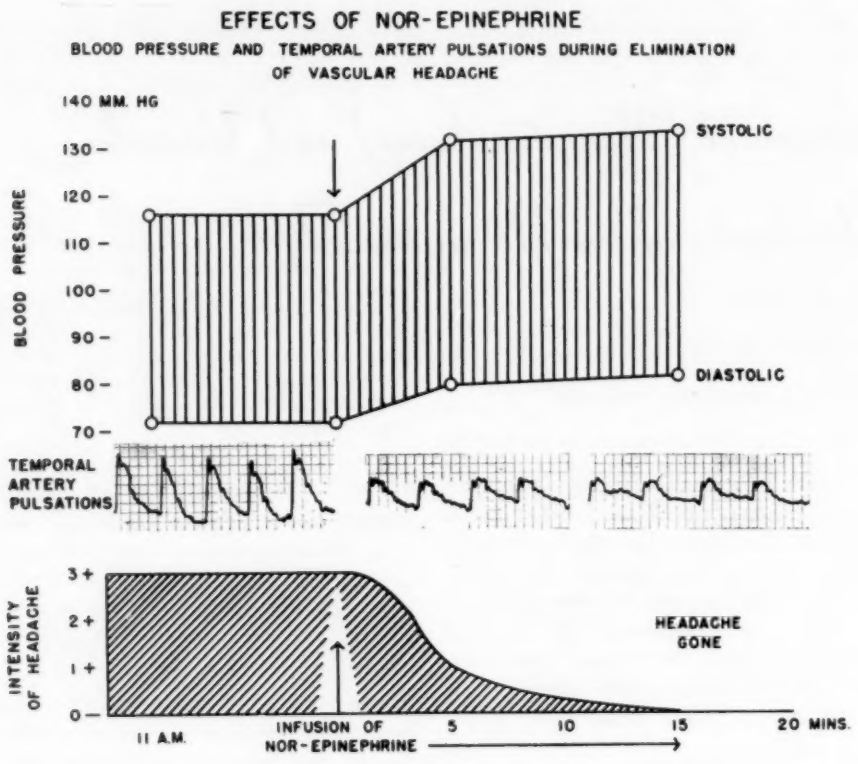


Figure 2

deep-pain dolorimeter. It was observed that the edema was decreased when a headache had been terminated through the action of arterenol. On three occasions the temporal artery was prominent enough that its diameter could be measured directly. As the headache intensity lessened, the diameter decreased. Pulse wave tracings showed a decrease in amplitude and increase in the number of reflected waves as the headache intensity was dwindling (Fig. 2). These contour changes had been observed previously by Wolff and Tunis [4] to be compatible with vasoconstriction.

Series 2.—Some of the migraine phenomena observed suggested the involvement of intraorbital or intracranial structures, and arterenol has been equally effective in modifying such disturbances. In a patient with ophthalmoplegic migraine manifested by diplopia and right sixth cranial nerve weakness, the ocular movements returned to normal and diplopia and strabismus disappeared after 70 minutes of arterenol infusion. In previous attacks in this patient the usual duration of sixth nerve involvement had been four days. Another patient who had ptosis of the right eyelid for 48 hours during a headache attack was able to raise the lid normally after 90 minutes of arterenol infusion. Irritability, giddiness, and difficulty in thinking were repeatedly eliminated during arterenol administration. Feelings of tension and exhilaration were common sequelae, and no depression, prostration, or lethargy was noted.

Series 3.—On seven occasions in four patients with essential hypertension of moderate severity, vascular headaches were similarly eliminated. Optimal effects were noted when arterenol was given at rates that induced an average rise in blood pressure of 28 mm. Hg systolic and 9 mm. Hg diastolic (Fig. 3).

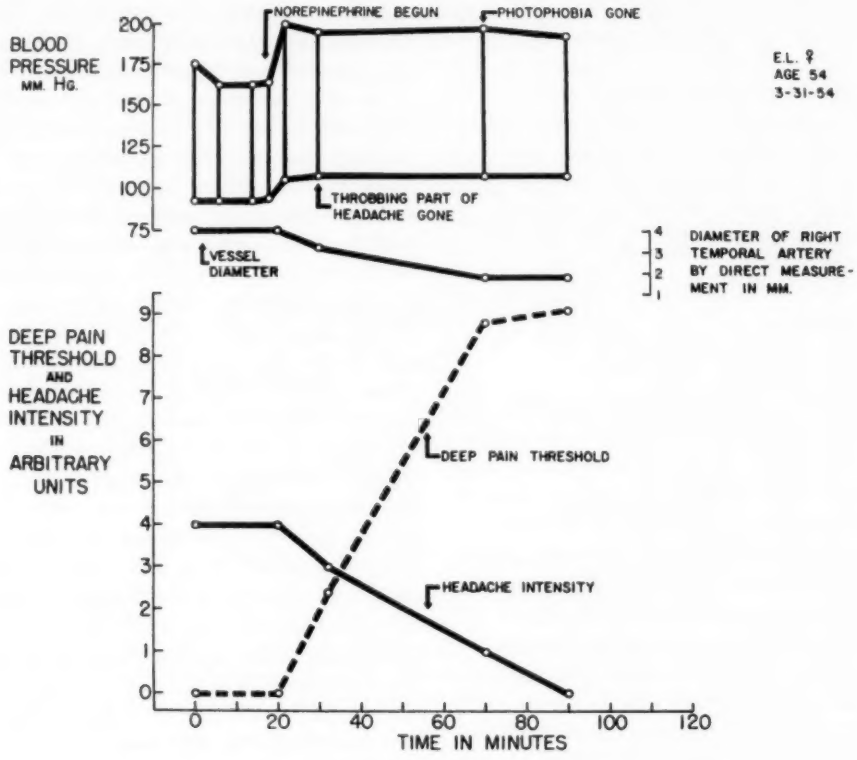


Figure 3

Comment

The amount of arterenol administered was under control at all times. Without ill effect, the agent was infused for as long as five hours. It was given as often as three times weekly to three patients. No nausea or vomiting resulted. The agent was used effectively after the administration of repeated ineffective amounts of ergotamine tartrate.

Certain untoward effects of arterenol have been observed. When it was infused too rapidly, there was a sudden, dramatic rise in blood pressure (40-60 mm. Hg systolic) with intensification of the headache already present, presumably due to distention of pain-sensitive intracranial arteries. Its administration therefore required the constant attention of competent personnel. Uncommonly, it produced unpleasant sensations in the neck with mild dysphagia. Muscle contraction headache, previously shown to be associated with scalp artery constriction, was increased.[6]

Series 4.—In an attempt further to elucidate the mechanism of vascular headache, the effects of arterenol and of ergotamine tartrate on deep-pain thresholds in scalp tissue were observed. In a previous communication it had been reported that lowered deep-pain thresholds of the scalp occurred in patients experiencing vascular headaches of the migraine type.[5] Further, it had been noted that pain thresholds were lowered first about the painfully involved large arteries, (i. e., supraorbital and temporal) and that lowered deep-pain thresholds persisted in many instances for hours or days after the spontaneous ending of a headache. When headache was terminated through the action of arterenol or ergotamine tartrate, the pain thresholds were raised more promptly than occurred when the headache ended spontaneously (Fig. 4). When headache was

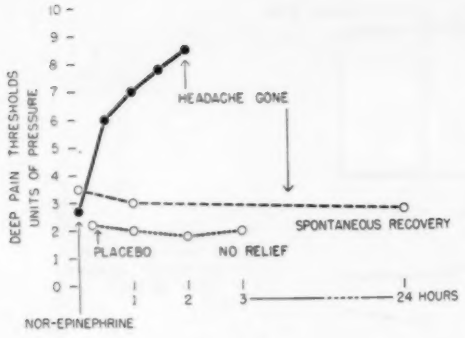


Figure 4

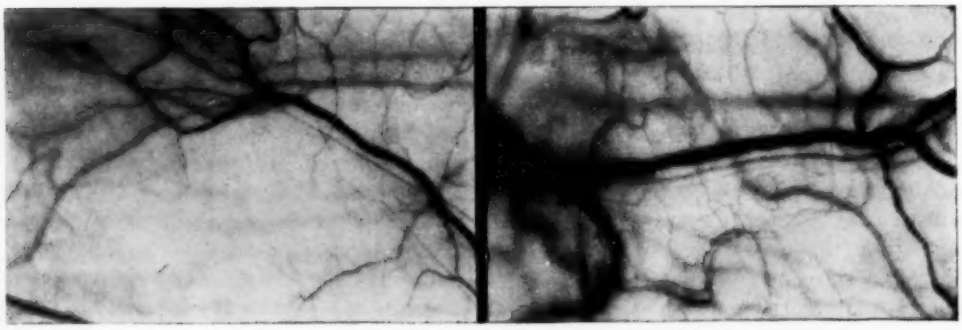
present in a small head area and deep-pain thresholds were lowered over a larger area, pain thresholds in the area involved with headache and in the area free of headache returned to preattack levels at the same rate during arterenol infusion. Moreover, when, after spontaneous ending of a headache, deep-pain thresholds remained lowered, the administration of arterenol or ergotamine tartrate raised them promptly. In following the dwindling intensity of headache after the vasoconstrictor drugs were given, it was noted that the deep-pain thresholds persisted at lower levels longer about the painfully dilated large arteries than in scalp tissue more peripheral to these vessels. In three instances when headache was allowed to end spontaneously and marked scalp edema was present, it was observed that deep-pain thersholds remained below preattack levels as long as edema persisted.

Series 5.—Armstrong and co-workers [7] have shown that there is a substance or substances common to serum and blister fluid which causes pain when these agents are deposited on the site of a blister base. When 0.4 to 0.5 cc. of serum was mixed with 300 T. R. units of commercial hyaluronidase and injected subcutaneously into the scalp, a burning and aching pain of moderate intensity appeared after a latent period of 15 to 30 seconds and persisted for 1½ to 3 minutes. The pain reached its maximum intensity within 10 seconds, remained at a plateau for 20 to 30 seconds, and slowly decreased in intensity. Ergotamine tartrate, when given parenterally in another site or mixed with the serum, had no effect on the pain-producing properties of the latter. However, when 0.05 to 0.1 mg. of ergotamine tartrate was diluted with 3 cc. of isotonic saline mixed with 300 T. R. units of hyaluronidase and injected into a scalp area involved with vascular headache, the headache was largely alleviated in 20 to 40 minutes. It is concluded that the effect of vasoconstrictor agents on deep-pain thresholds is attributable not to neutralization of any pain-producing substance in serum but to their removal from tissues into the blood stream via vasoconstriction.

GENERAL COMMENT

The following postulated mechanism of vascular headache and of the effect of vasoconstrictor agents is in keeping with the foregoing observations. At the onset of headache there is concomitant dilatation of the large arteries, arterioles, and metarterioles (Fig. 5). The dilatation of the arterioles

Figure 5



and metarterioles increases the capillary hydrostatic pressure. Since capillary osmotic pressure remains constant, water and all substances of relatively lower molecular weight in plasma filter into the subcutaneous tissue in greater-than-normal amounts. Furthermore, the elevated capillary hydrostatic pressure favors the accumulation of these substances in the subcutaneous tissue of large arteries coupled with accumulation of this pain-threshold-lowering substance result in headache.

It is also suggested that when headache spontaneously ends, the large arteries constrict while the arterioles and metarterioles remain dilated. Thus, some of the pain-threshold-lowering substance and fluid is retained in the tissue. This explains the repeat-

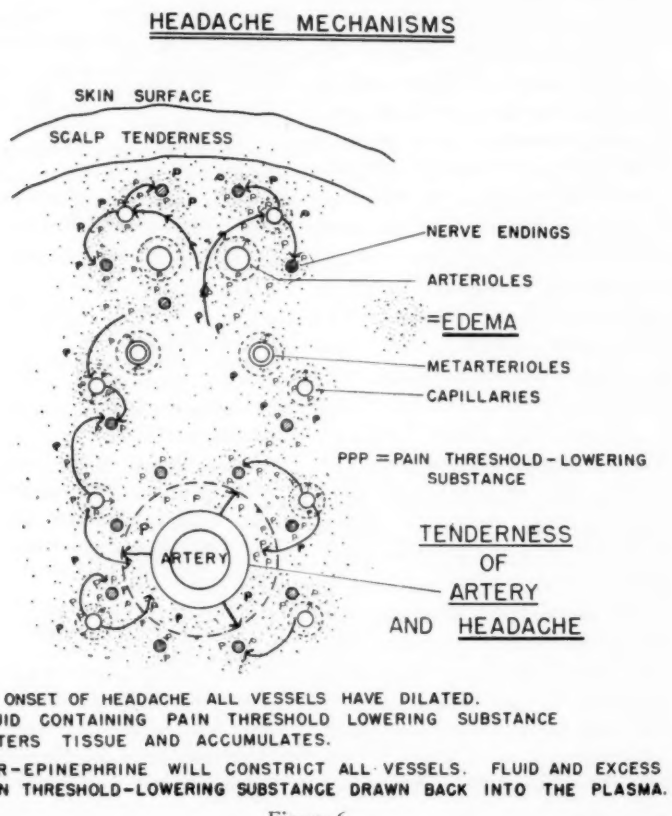

HEADACHE MECHANISMS
SKIN SURFACE
SCALP TENDERNESS
NERVE ENDINGS
ARTERIOLES
=EDEMA
METARTERIOLES
CAPILLARIES
PPP = PAIN THRESHOLD - LOWERING SUBSTANCE
ARTERY
TENDERNESS OF ARTERY AND HEADACHE
1. AT ONSET OF HEADACHE ALL VESSELS HAVE DILATED. FLUID CONTAINING PAIN THRESHOLD LOWERING SUBSTANCE ENTERS TISSUE AND ACCUMULATES.
2. NOR-EPINEPHRINE WILL CONSTRICT ALL VESSELS. FLUID AND EXCESS PAIN THRESHOLD-LOWERING SUBSTANCE DRAWN BACK INTO THE PLASMA.

Figure 6

the scalp. There is thus present in the tissue in greater amounts than normal a substance, postulated as "P" substance, that lowers deep-pain thresholds (Fig. 6). The precise nature of this "P" substance, so closely linked with vasodilatation, is ill-defined, but it is probably related to the pain-threshold-lowering substances in blister fluid. Among its other properties, it has the capacity of damaging tissue and overcoming vasoconstriction. Dilatation and distention of

edly made observation that scalp edema outlasts headache and that deep-pain thresholds may be delayed hours or days in returning to normal after headache ends spontaneously.

With the administration of arterenol, arterioles and metarterioles constrict, the capillary hydrostatic pressure lowers, and plasma osmotic pressure now becomes more effective in the reabsorption of extracellular fluid. Accumulated pain-threshold-lowering substance is thus pulled out of the tissue, and

promptly the pain threshold rises to pre-attack levels. Almost at the same time the painfully dilated large arteries constrict and the headache attack is terminated.

The investigations of von Euler and others have shown that arterenol is the substance mediating the effects of stimulation of adrenergic nerves.† It has been further shown that arterenol acts almost entirely as a vasoconstrictor and does not share with epinephrine the ability to produce marked metabolic changes.‡ While ergotamine tartrate is also a vasoconstrictor, it has other effects, notably on the central nervous system. Thus, it is possible that the vasoconstrictor property of the ergot alkaloids is not the only effective one in the treatment of migraine. However, the fact that an almost pure vasoconstrictor agent, such as arterenol, promptly reverses all the painful aspects of migraine headache is further evidence that the genesis of this pain is vasodilatation, granting that local tissue changes do lower the pain threshold so as to make vascular distention more painful.

SUMMARY AND CONCLUSIONS

Arterenol, an agent with almost pure vasoconstrictor and minimal metabolic effects, has been shown to terminate migraine headache promptly, and to reverse evidence of increased tissue vulnerability more rapidly than occurs spontaneously. Observations herein noted suggest that the constricting effect on relatively larger vessels and on arterioles and metarterioles terminates headache and raises deep-pain thresholds. The latter process is presumably effected by drawing a pain-threshold-lowering substance out of tissue and back into the blood.

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‡ References 12 and 13.

The Capillary System in Patients with Psychiatric Disorders

Increased "Capillary Blood Pressures" in Neurosis and Psychosis and Its Relation to Some Correlates of Anoxemia

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Peripheral circulatory anomalies are notoriously common in mentally ill patients; they exist at the levels of structure and function and both at rest and in dynamic settings under stress. Clinically, the puffy, raw-beef, violaceous hands of some schizophrenic patients contrast vividly with the white, baby-soft, transparent peripheral pallor of others. In other psychiatric disorders, Raynaud-like syndromes are seen, and dermatographism, all grades of cyanosis, excessive sweating, marbled appearance of the skin, and disordered temperature control are frequently noted on physical examination. Experimentally, the morphological study of the skin capillaries by capillary microscopy has indicated structural peculiarities of these vessels sufficiently obvious to differentiate psychiatric patients from those in mental health, while techniques of finger plethysmography, oximetry, skin resistance, electromyography, and skin thermometry applied to such patients afford physiological examples of similar methods of differentiation. Some of the literature on these peripheral vascular anomalies has been recently reviewed (Abramson,[1] 1944; Shattock,[32] 1950; Lovett Doust,* 1951 and 1952).

Evidence is accumulating which suggests that the oxygen metabolism of patients with certain mental disturbances shows impairment (Hoskins,[12] 1946; Danziger and Kindwall,[7] 1953; Freyhan and associates,[8] 1951) and that this impairment does not always show up in the analysis of blood from large peripheral vessels (Looney and Freeman,[20] 1938; Segal and Hinsie,[31] 1926) or even from blood vessels in close relationship to the brain (Myerson and Halloran,[30] 1930; Kety and associates,[13] 1948); it is, however, apparent as an anoxemia in histochemical studies on the hemoglobin of the red cells (Tsikhanshkaya,[34] 1948) and at the level of capillary function (Lovett Loust,† 1951 and 1952; Lovett Doust and associates,[27] 1953). A study of the capillary system in psychiatric patients would seem, therefore, to hold out promise of learning more of the pathophysiology of this group of disorders, and the growing literature on capillary structural anomalies common to such a group presages a rich harvest of possible functional disturbances. An essay in this field has already been attempted (Lovett Doust,‡ 1955), and the present communication, dealing with variations in capillary blood pressure, was suggested by the work of one of Sir Thomas Lewis' associates (Briscoe,[3] 1918) on a class of patients with a condition now believed to be closely related to psychoneurosis.

METHOD

The indirect method of estimating capillary pressure followed that used by Briscoe[3] in her study

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* References 21 and 23.

† References 22 and 23.

‡ References 24, 25, and 26.

of cases of neurocirculatory asthenia. A glass capsule was blown in accordance with Hooker's [11] (1914) specifications for his venous-pressure apparatus. The capsule measured 20 mm. in diameter, was 10 mm. high, and was made from glass 1 mm. thick. A small tapered glass tube was heated in at the side and served to connect the capsule with a water manometer, the scale of which was graduated in 1-cm. steps up to 70 cm. A T-connection enabled the air pressure inside the chamber to be increased at will by means of a manually operated rubber bulb and simultaneously to influence the pressure in the manometer. Before the capsule was attached to the subject's hand, it was found by experience to be desirable that the free edge of the glass be treated by several coats of collodion, each being allowed to dry before the next was applied. In this way a wider area was made available for attachment to the skin than was possible when the thin glass edge was used alone.

The capsule was pressed against the dorsum of the subject's hand, care being taken to avoid any obvious veins in this area, and fixed in place by the generous application of more collodion. Pressure was continued until the preparation was quite dry, and the apparatus was tested to ensure complete airtightness. The subject was then seated comfortably, his hand, forearm, and elbow resting on the bench and on a level with his subcostal angle. Illumination was held constant, and all observations were made in the afternoons, between 2 and 4 p. m. The capillary blood pressure was taken to be that pressure recorded on the manometer scale at which blanching of the skin beneath the capsule occurred, a further rise in air pressure producing no additional blanching. A series of readings was always taken, never less than six, and often two or three times this number, until consistent estimates were obtained.

CLINICAL MATERIAL

A total of 167 subjects was investigated. Of these, 67 were healthy controls, mainly conscript soldiers drawn from all walks of life and aged between 18 and 46 years. One hundred were mentally disturbed patients, some of whom were also military personnel, while the rest were civilian inpatients of a psychiatric hospital. The abnormal group included 12 patients with psychopathic personality; 41 with psychoneurosis (including 20 cases of chronic anxiety state and 21 of hysteria; 17 with affective disorder, all in a depressive phase of their illness; 27 with schizophrenia (including 16 "constitutional" schizophrenics with hebephrenia, catatonic schizophrenia, or dementia praecox simplex, and 11 "paranoid" schizophrenics), and 3 patients with presenile dementia (2 with Alzheimer's disease and 1 with Pick's disease). The age range of the patients lay between 18 and 62; the sex ratio was approximately unity. All patients, both military and civilian, had been examined by two or more competent psychiatrists; the former group were all considered sufficiently disturbed to warrant recommendation that they be invalided out of the service, the latter group sick enough to warrant hospitalization.

RESULTS

Healthy Control Group.—Validation of the Methodology: The method yielded a mean capillary blood pressure among the 67 healthy subjects of 26.78 cm. of water and a range of 16-42 cm. (standard deviation =7.034). Landis [17] (1930), who employed a microinjection technique of measurement on the capillary loops to the fingernail fold, found values for his subjects which varied according to which limb of the loop was cannulated. His mean for the arteriolar limb was 44 cm. of water (range=29–65 cm.), that for the venous limb being 16 cm. of water (range=8–25 cm.). Cannulation at the summit of the loop, however, yielded values intermediate between these two, with a mean of 27 cm. of water (range=20–44 cm.). Unfortunately, no actual protocol data or any standard deviations are given in his paper, so that it is difficult to make exact comparisons; but his value for the summit of the loop and ours by the indirect method resemble one another very closely both in their means and in their ranges.

Further confirmation of this is given by a comparison of our results with those of Briscoe's [3] healthy control subjects. Using a much smaller group but an identical technique, she reported a mean capillary pressure of 24 cm. of water (range=20–26 cm.). Such results are in line also with those of the older workers, who employed other modifications of the skin-blanching method of estimation and who obtained ranges of capillary blood pressure of 17 to 28 cm. of water (von Kries,§ 1875), 18 to 22 cm. (von Bach,‖ 1900) and 13 to 18 cm. of water (Landerer,[15] 1913).

§ von Kries,[36] cited by Landis.[18]

‖ von Basch,[35] cited by Landis.[18]

Landis himself states [18] (1934) that the microcannulation method is unsuited to clinical use, and it may therefore be concluded that the measurement of the capillary blood pressure by the indirect Hooker capsule technique is a valid one for routine use, at least in the circumstances in which it was employed here, and that the values obtained correspond with those obtained by Landis [17] (1930) for the pressure at the summit of the nail fold capillary loop.

Influence of Psychiatric Diagnosis on Capillary Pressure.—Briscoe [3] was the first to show that if the capillary blood pressures of healthy subjects are compared with those of "nervous" patients, the pressures of the latter group are found to be significantly raised. The work of Cobb [4] (1946) and others has proved fairly conclusively that patients with irritable heart (or "D. A. H."), who constituted Briscoe's experimental nervous group in World War I, and those with a condition variously diagnosed as effort syndrome, da Costa's syndrome, or neurocirculatory asthenia in World War II, are really examples of a psychiatric disturbance, i. e., anxiety state. If this is so, then it would be anticipated that capillary-pressure disturbances might not be confined to any one particular mental illness but would be reflected in other psychiatric disorders.

Table 1 shows this to be so. It demonstrates, first, a mean capillary blood pressure in patients with psychoneurosis-anxiety state which is sensibly greater than that of a comparable series of healthy subjects, and, second, that the mean pressures of all the psychiatric patients are raised. But it also shows more than this: It suggests that the capillary pressures of patients with both forms of neurosis and those of psychopaths, depressives, and paranoid schizophrenics are roughly equivalent, while those of "constitutional" schizophrenics are raised above the levels of this group of patients and those of the organic dements are increased even higher. In other words, the capillary pressure determinations form a spectrum along which psychiatric patients may be placed in accordance with the severity of their mental disturbance. It is interesting, also, that the statistical tests employed in the evaluation of these results show them to possess highly differentiating significance.

TABLE 1.—*Scatter of the Means in Eight Psychiatric Diagnostic Groups*

Diagnostic Group	N	Capillary Pressure* Group Means, Cm. Water	Capillary Pressure* σ	Analysis of Variance
Healthy controls	67	26.776	7.034	
Psychopathic personality	12	33.417	6.374	
Psychoneurosis				
Anxiety state	20	33.850	6.963	F ratio: 4.388
Hysteria	21	34.476	6.418	$d.f.$: 7 and 159
Affective disorder				
Depression	17	29.118	4.920	P: <0.001
Schizophrenia				
Constitutional	16	37.370	15.907	$\eta^2 = 0.162$
Paranoid	11	30.729	8.822	
Organic dementia	3	47.667	2.511	

* Capillary blood pressure (skin-color-disappearance pressure) measured by the Hooker capsule technique.

Effect of Age.—So far as can be ascertained from the literature, no data exist as to the effect of age on capillary pressure. Because of this, and because of the slight disparity of age between the control and the psychiatric groups, it was decided to undertake an examination of the possible influence of this variable on the findings. Table 2 records the results of a two-way analysis of variance, in which the separate influences of the factors of age and diagnosis are considered together and then the differential contributions of the two factors are compared for significance. As can be seen from the Table, age and diagnosis together contribute 22% to the variance of the means.

TABLE 2.—*Two-Way Analysis of Variance Applied to Diagnostic Group Means of the "Capillary Pressure" Estimations and Illustrating Lack of Significance of Chronological Age*

Age Range, Yr.	Diagnostic Group	N	Capillary Pressure, Cm. Water: Mean	Capillary Pressure, Cm. Water: σ	Analysis of Variance
Up to 19	Healthy controls	10	27.300	4.832	1. Diagnostic Group
20-27		36	27.000	4.900	+ Age
28-35		14	23.714	4.746	
36 and over		7	31.000	9.129	F ratio: 3.932
Up to 19	Psychopathic personality and psychoneuroses	17	33.647	6.244	$d.f.$: 11 and 155
20-27		24	34.917	5.679	
28-35		8	34.625	6.186	P: <0.001
36 and over		4	31.250	6.397	
Up to 19	Psychoses and organic dementia	6	35.333	6.532	η^2: 0.219
20-27		16	36.062	13.061	
28-35		12	35.250	12.969	
36 and over		13	36.384	14.082	
Up to 19	Age only	33	32.030	6.649	2. Age Only
20-27		76	31.408	8.487	F ratio: 0.775
28-35		34	30.353	10.242	$d.f.$: 3 and 163
36 and over		24	33.958	12.034	P: N. S.
					η^2: 0.014
Diagnosis only	Controls	67	26.776	5.859	3. Diagnosis Alone
	Psychopathic personality and neuroses	53	34.188	6.074	F ratio: 18.821
					$d.f.$: 2 and 164
	Psychoses and organic dementia	47	35.851	12.344	P: <0.001
					η^2: 0.187
	4. Addition of Age to Diagnostic Group				F ratio: 0.694 P: N. S.

The individual contribution to this of diagnosis amounts to nearly 19% of the variance, however, and the additional variance contributed by age alone is statistically not significant. It is apparent, therefore, that chronological age, at least within the range of 18 to 62 years, does not significantly influence capillary pressure as measured by the Hooker capsule technique.

Relationship of Capillary and Arterial Blood Pressures.—Capillary blood pressure is potentially related to the arterial blood pressure in the sense that it represents a gradient of pressure (Lewy,[19] 1897; Dale and Richards,[6] 1919) from it which continues throughout the capillary network. Landis [17] (1930) has shown this to be true for man as well as for lower animals, and he has demonstrated that in exposed tissues, such as the skin, 20% to 30% of the peripheral resistance to blood flow is located in the capillaries. In four species, including man, studied by Landis [18] the average capillary pressures obtained by his microcannulation technique were approximately equivalent to the colloid osmotic pressure of the plasma proteins.

At the time the observations currently reported were made, it was not possible to run simultaneous estimations of the plasma osmotic pressures. It was, however, practicable to investigate the possible relationship of the arterial pressure to the capillary blood pressure, and hence circumstantially to the osmotic pressure of the plasma proteins. Accordingly, immediately prior to the capillary pressure estimations on 156 of the 167 subjects, the arterial blood pressure was measured and the results of the capillary and arterial pressures intercorrelated. The product moment correlation coefficient resulting from this procedure ($r=+0.110$) indicated a lack of significant relationship between these two variables, and this result was considered further confirmation of the conclusions of Bayliss and Starling [2] (1894) as to the essential independence of these twin factors.

Relationship of Anoxemia to Capillary Blood Pressure.—Though relatively unchanged by excessive carbon dioxide, capillary permeability is greatly increased by anoxemia (Landis,[16] 1928; Starr [33] 1925), and it is also known that factors influencing

permeability are dependent to a significant extent upon the capillary pressure variable (McMaster and associates,[28] 1932). Oxygen passes through the capillary wall to reach the tissues by a process of simple diffusion. Temporary hypoxia induces an increased capillary blood flow and, according to Krogh[14] (1929), the opening up of many quiescent capillary loops, thus resulting in a reactive hyperemia. Should tissue anoxia persist in spite of these homeostatic efforts to combat it, protein transudation into the tissues takes place and edema results. Although Landis stated ¶ that the "effects of oxygen lack, if sufficiently brief in duration, are almost completely reversible," he also notes that little information is available concerning the importance of long-continued, mild oxygen lack.

It was mentioned, in the introduction to the present communication, that edema and cyanosis were characteristic features of the hands of certain patients with psychiatric disturbances, and it has also been shown (Lovett Doust,# 1951, 1952, and 1955) that capillary anoxemia is characteristic of such patients, both at rest and in states of emotional unrest. It appeared of interest, therefore, to undertake an analysis of capillary pressure in terms of some variables relating to capillary oxygen saturation levels.

The first procedure was to correlate the capillary pressure measurements with the results of spectroscopic oximetric estimates of the capillary oxygen saturation made on 158 of the same group of healthy subjects and psychiatric patients. The oximetric measurements were taken from the capillary vessels of the skin of the fingernail fold; the capillary blood pressures, from the skin of the dorsum of the same hand. The oxygen saturation values ranged from 89.5%, in the patients, up to 100%, in the controls.

A product moment correlation coefficient which was run on these two factors revealed a probably significant degree of interdependence between them (r=—0.167; t=2.117; $d.f.$=156; P=0.05). The negative sign of the correlation coefficient indicates that high capillary pressures are associated with a tendency toward capillary anoxemia, while pressures within the normal range are associated with an average normal blood oxygen saturation.

A second procedure was also undertaken. In 91 of the massed controls and patients a gross estimate was made of the capillary hemoglobin level by comparing the color of the blood in the capillaries of the fingernail fold, as visualized by microscopy, with the color chart of the Tallqvist scale. The range of "hemoglobin" levels obtained in this way lay between 40% and 75%, and a product moment correlation coefficient run on these results and those of the capillary pressure estimations revealed a close association between them (r=0.629; t=9.825; $d.f.$=89; $P<0.001$).

Relationship of Capillary Fragility to Capillary Blood Pressure.—A final point of interest arises out of Cohnheim's original microscopic observation[5] (1867) that extracapillary hemorrhages can be seen appearing in the web of the frog's foot following venous congestion. Cohnheim postulated the presence of potential gaps in the continuity of the capillary wall which are patent to red cells under conditions of vasodilatation but which disappear when vascular tonus is restored. Microinjection of India ink into single capillaries of the frog's mesentery by Landis * (1934) confirmed these findings, and this worker remarked † that "the relation of capillary permeability to mild, long-continued oxygen lack and to these temporary openings will probably explain certain perplexing anomalies of fluid movement during tissue activity."

As has been emphasized already, it is at the capillary level of function that long-continued oxygen lack characterizes certain patients with psychiatric disorder (Lovett Doust ‡), and such patients have already been found to possess thresholds of capillary fragility significantly lower than those of

¶ Landis,[18] p. 462.

References 22, 23, and 25.

* Work cited in Landis.[18]

† Landis,[18] p. 464.

‡ References 22 and 23.

healthy subjects (Lovett Doust,[26]). It was therefore deemed of interest to ascertain the relationship between such capillary fragility thresholds and the capillary pressure.

Capillary fragility was measured by the Göthlin § positive-pressure technique, as standardized by Munro, Lazarus, and Bell,[29] (1942), and with the skin of the antecubital fossa as the site of examination. A correlation coefficient determined on the results of these two investigations in 157 healthy subjects and psychiatric patients revealed that capillary resistance is indeed a function of capillary pressure, extravasation of blood occurring progressively more commonly as the hydrostatic pressure in the capillaries increases. The results were statistically highly significant ($r=0.604$; $t=9.435$; $d.f.=155$; $P<0.001$).

SUMMARY

Determinations of capillary blood pressure were made by the indirect Hooker capsule technique on 67 healthy (control) subjects and on 100 patients with a variety of psychiatric disorders. The site of examination was the skin of the dorsum of the hand.

It was found that the results of this clinical method were similar to those of the direct microintubation technique and gave a mean capillary pressure of 26.776 cm. of water in the case of the control subjects.

Capillary pressure was found to be significantly higher in the psychiatric patients than the value for the control subjects, however, results for organic dements and psychotics being greater than those for neurotics and psychopaths. The possible influence of age, within a wide adult range, was studied and found to be statistically insignificant.

Correlations between capillary blood pressures and a number of possibly related variables revealed a lack of relationship with the systolic arterial pressure, but significant interdependence with oximetrically monitored percentage capillary oxygen saturation, capillary hemoglobin levels, and capillary fragility as estimated by the positive-pressure method.

The implications of these findings in terms of the vascular anomalies of psychiatric patients are discussed.

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Incidence of Seizures, with EEG Findings, in Prefrontal Lobotomy

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This study endeavors to add further objective data to the incidence and course of seizures as a complication of prefrontal lobotomy, with electroencephalographic (EEG) findings and their relationships to the clinical results.

METHOD

A survey of the occurrence of seizures as to type, time after lobotomy, frequency, and course was made on 193 prefrontal lobotomies in 181 patients from March, 1946, to May, 1954, at the Veterans Administration Hospital, St. Cloud, Minn. Anticonvulsant medication was not given to patients who were seizure-free prior to the operation unless the convulsions occurred at a minimum of three regular intervals or were persistent. The EEG's were taken before and within 10 days after the lobotomy. Thence they were taken serially, insofar as possible, at intervals of a month for six months and at six-month intervals thereafter. The recordings were made on a Grass machine with monopolar leads on six channels to December, 1953, and subsequently on eight channels. To aid in accuracy, readings were made by two different interpreters, using the classification of Gibbs, Gibbs, and Lennox.[6] Follow-up reports were made on those patients who left the hospital. A brief general report was made on incidence of seizures with EEG findings on the first 100 lobotomized patients in a previous publication.[12] The present EEG results with their relationships are based on 100 patients, of whom 83 were followed for a minimum period of six months, between August, 1949, and February, 1955. A method of numerical classification of the severity, type, and frequency of EEG abnormalities was used similar to that of another current study.[11] A modification of this method was used in that the persistence of the abnormalities was classified as Grade 1, 2, and 3, corresponding to the length of time as less than three, less than six, and over six months, respectively. A total of 940 EEG's were taken on this series of 100 patients.

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With the technical assistance of Gilbert Lommel, EEG technician.

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FINDINGS

1. *Seizures.*—These were primarily of the grand mal type and occurred in 36 patients

TABLE 1.—*Frequency of Seizures and Course in Previously Epileptic and Nonepileptic Patients After Lobotomy*

Epileptic				Nonepileptic			
Frequency				Self-Limiting		Persistent	
Before Lobot.	After Lobot.	Status	No. of Patients	Total No.	No. of Patients	Frequency	No. of Patients
Infreq.	None	Better	..	1	11	Occas.	7
9 × yr.	Infreq.	Better	..	2	7	3 × yr.	1
2 × mo.	Infreq.	Better	..	3	3	4 × yr.	1
1 × wk.	1 × mo.	Better	4	..	..	6 × yr.	4
1 × mo.	1 × mo.	Same	..	..	..	12 × yr.	1
3 × yr.	3 × yr.	Same	2	..	..	1 × wk.	1
2	3	Worse	..		—		—
Rare	6 × yr.	Worse	..	Total	21		15
Occas.	1 × yr.	Worse	3				
			—				
	Total.....		9				

TABLE 2.—*Relation of EEG's to Clinical Results from Lobotomy*

Degrees of Improvement	None	Slight	Moderate	Marked	?	Total
Grades	3; 4; 5	2c	1c; 2b	1a; 1b; 2a		
EEG's						
Normal	1	6	5	2	0	14
Slightly abnormal	5	11	15	6	1	38
Moderately abnormal	2	9	6	2	0	19
Severely abnormal	8	7	9	5	0	29
No. of patients	16	33	35	15	1	100

TABLE 3.—*Percentage Relationship of Better Types of Clinical Improvement from Lobotomy to EEG Findings*

Clinical Improvement	EEG Findings, Per Cent			
	Normal	Slightly Abnormal	Moderately Abnormal	Severely Abnormal
Moderate or marked	50	55	42	49

who were previously free from convulsive disorders. Several patients had occasional syncopal attacks, but these were not included. Nine patients (including two with seizures due to the first lobotomy) with seizures prior to the operation continued to have them, with one exception, who became seizure-free. The incidence of these seizures occurring for the first time postoperatively is recorded in Graph 1. The seizures were classified according to course in Table 1, and the patients who were previously seizure-free were subdivided into the groups with self-limiting and the group with persistent seizures. There was no causal relationship of any significant degree between the number of grand mal seizures from previous electrotherapy and the incidence of seizures, with the exception of a few patients who had a large number of treatments.

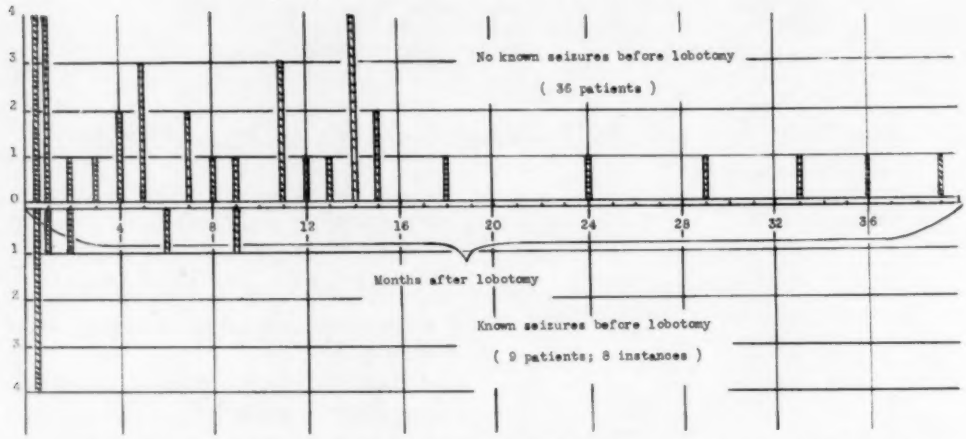
2. EEG Findings.—The number of abnormal EEG'S taken before and serially after lobotomy are charted in Graph 2. The relationship to clinical results of prefrontal lobotomy is presented in Table 2. The method of grading of clinical results has been discussed in the previous study.[12] The relationship of the EEG findings to the better degrees of clinical improvement is presented in Table 3. Most of the focal abnormalities were located in the frontal areas, with a predilection for the right frontal. These consisted primarily of slow waves (S-3) type, with a tendency to alternate in the frontal leads, and paroxysmal activity. Paroxysmal activity was noted in 9 (21%) out of 41 patients with clinical seizures and in 16 (18%) out of 87 patients without evidence of seizures.

COMMENT

Postoperative seizures occurred for the first time after intervals varying up to 39 months in the nonepileptic group and up

TABLE 4.—*Focal and Generalized EEG Abnormalities*

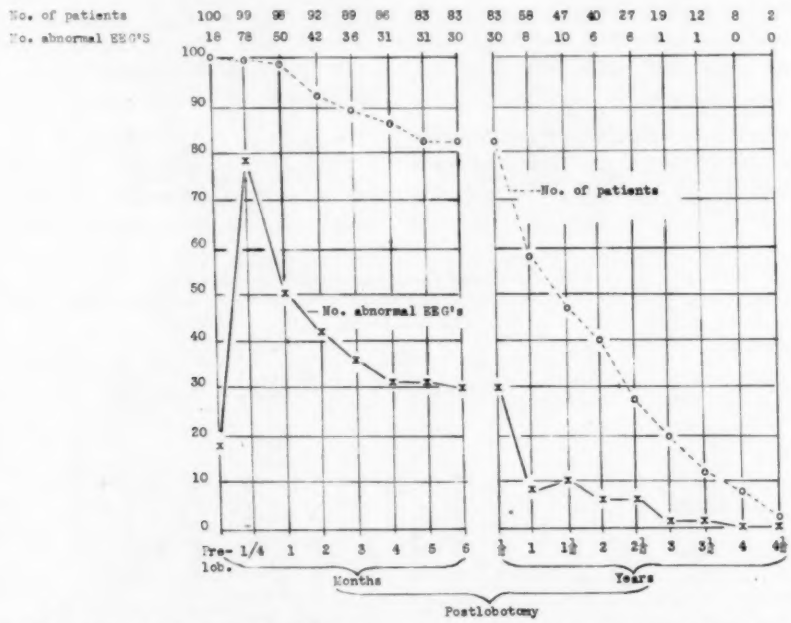
	EEG Abnormalities												
	Focal											Total Generalized	Total
	Frontal				Parieto-Occipital			Hemisphere			Right Temporal		
Types	Both	Alternating	Right	Left	Right	Left	Alternating	Right	Left	Alternating			
Slow waves	13	19	31	13	0	1	1	3	4	1	0	86	4	90
Paroxysmal	4	0	4	0	1	0	0	0	1	0	1	11	7	18
Total												97	11	108


No known seizures before lobotomy
(36 patients)
Months after lobotomy
Known seizures before lobotomy
(9 patients; 8 instances)

Graph 1.—Occurrences of seizures for first time after lobotomy in patients with and without known seizures before lobotomy.

to 9 months in the epileptic group (Graph 1). The fact that one of the latter was seizure-free after the operation would indicate that freedom from emotional turmoil may have been the ameliorating factor. The incidence of convulsions in the 36 patients, previously seizure-free, including 4 who had no seizure after the first lobotomy, constituted 19% of the total number (193) of lobotomies. However, 21 (59%) of these patients had self-limiting seizures, and almost half of the remaining 15 patients with persistent seizures had them only upon occasion (Table 1). The general incidence of seizures in various studies * varied from 3.3% to about 26% in single lobotomies and

* References 2, 3, 4, 5, 7, 8, 10, 12, 16, 18, and 19.


No. of patients 100 99 96 92 89 86 83 83 83 58 47 40 27 19 12 8 2
No. abnormal EEG's 18 78 50 42 36 31 31 30 30 8 10 6 6 1 1 0 0
No. of patients
No. abnormal EEG's
Pre-lob. 1/4 1 2 3 4 5 6
Months
½ 1 1½ 2 2½ 3 3½ 4 4½
Years
Postlobotomy

Graph 2.—Number of abnormal EEG's in current number of patients serially after lobotomy.

up to 47% in multiple operations or with complications. The severity of the seizures in the epileptic group is considered to be somewhat ameliorated by the operation (Table 1). There was an apparent relationship between the number of grand mal seizures, especially in patients who had over 100, from electrotherapy and the subsequent seizures, agreeing with Greenblatt and associates,[8] who thought that patients with "many" grand mal attacks were more likely to develop convulsions.

The incidence of abnormal EEG'S increased rapidly from 18% preoperatively, most of which were due to electrotherapy, to 78% in the immediate postoperative period. The rapid decrease of abnormalities by the fourth month, with further progression in that direction, seems to be a fairly common finding (Graph 2). It is interesting to note that 14, including 2 patients followed for five months and not included in the series, had normal EEG'S before and after the operation. Eighteen more patients had abnormalities limited primarily to the first postoperative month. This would suggest that most of the latter had reversible EEG changes due to the temporary disturbance of brain physiology. This seems to reflect on the theory that functional isolation of the prefrontal cortex from the rest of the brain may cause large groups of cells in the former to discharge synchronously.[9] The prevalent EEG abnormality of slow waves (primarily S-3) in the frontal areas has also been found by other investigators.† Contrary to the findings of Greenblatt and associates,[8] there was little difference between the incidence of paroxysmal abnormalities in the group of patients who did or the group did not have clinical seizures after lobotomy. Two patients who died in status epilepticus, 5 and 11 months, respectively, after operation, had no previous seizures and the EEG findings showed no notable abnormalities. The lack of direct relationship between the degrees of EEG abnormalities and clinical results from lobotomy has also been noted by others.‡ Contrary to the findings of Adler and Talbot,[1] but similar to those of Lennox and Coolidge,[14] the sleep spindles were diminished in the frontal leads but were frequently noted in the parietal leads, usually at rate of 12 to 14 per second.

† References 7, 8, 9, 12, 14, 17, 18, and 19.

‡ References 15 and 18.

SUMMARY

A survey of the incidence of seizures and EEG findings was made in 181 patients subjected to 193 prefrontal lobotomies at the Veterans Administration Hospital, St. Cloud, Minn., in a period from March, 1946, to February, 1955.

Seizures were primarily of the grand mal type and occurred in 36 patients, previously seizure-free, constituting 19% of all lobotomies. The convulsions were self-limiting in 21 (59%) of this group, and nearly half of the remaining 15 patients (8% of all the lobotomies) had only occasional persistent seizures (Table 1).

In general, the seizures tended to improve in the nine epileptic patients subjected to prefrontal lobotomy, and one of these patients had no further seizures after the procedure (Table 1).

Seizures occurred for the first time most frequently in the immediate postoperative period. The interval varied from a maximum of 9 months in the epileptic group to 39 months in the nonepileptic group (Graph 1).

Anticonvulsant medication was not given to patients previously seizure-free until seizures occurred at a minimum of three regular intervals or were persistent irregularly.

EEG'S were taken before and serially after lobotomy in a series of 100 patients consecutively fulfilling the stated criteria, from August, 1949, to February, 1955.

EEG abnormalities were observed in 18% of the patients before lobotomy, most of which were due to effects of electrotherapy.

The abnormalities increased to 78% in the immediate postoperative period, rapidly improved in the next four months, leveled

off, and improved again until there were no abnormal EEG'S in the patients current at the fourth postoperative year (Graph 2).

The types of abnormalities were primarily of the S-3 type (1 to 3 waves per second) and were located most frequently in the frontal areas.

Focal abnormalities seemed to predominate in the right frontal area, with some tendency to alteration of the focus to the left.

There was little significant relationship of abnormalities of the EEG to clinical results and incidence of seizures.

There was an apparent relationship between the large number of grand mal seizures from electrotherapy and the increased incidence of seizures after lobotomy.

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Blood-Brain Barrier and Ground Substance of Central Nervous System

Effect of Brain Wounds

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A positive periodic acid-Schiff reaction occurs between the cell bodies in the gray matter of the adult central nervous system. Since this reaction is not exhibited by neuroglia fibers, nerve processes, or cell bodies, it has been suggested that there is an additional element in the central nervous system, the ground substance, which is probably of a carbohydrate-protein nature (Hess,[5] 1953). Trypan blue, administered intravenously or intraperitoneally, is a valid test substance for the presence or absence of a blood-brain barrier (King,[10] 1939). Intravenous trypan blue does not stain the adult brain (Goldmann,[4] 1913), indicating the presence of a blood-brain barrier. On the other hand, intravenous trypan blue stains the brains of several newborn animals (Behnsen,[1] 1927; Stern and Peyrot,[15] 1927; Penta,* 1932), indicating the absence of a blood-brain barrier. The mouse brain stains easily and extensively with trypan blue until 2 weeks of age, at which time the storage of trypan blue in the brain begins to decrease (Behnsen,[1] 1927). It has been shown that the ground substance, or periodic acid-Schiff-reactive material, of the mouse brain is absent, or present only in reduced amounts, until 2 weeks of age, when it becomes similar in appearance and quantity to that of the adult brain (Hess,[7] 1955). Similarly, the newborn guinea pig brain does not stain with intravenous trypan blue and already has a blood-brain barrier (Stern and Peyrot,[15] 1927; Broman,[2] 1941), probably because the ground substance of the guinea pig brain is present already in the fetus at 45 days of gestation and assumes proportions similar to that in the adult brain at 50 days' gestation age (Hess,[6] 1955). Thus, the absence or presence of a blood-brain barrier and the consequent ability of the brains of animals to stain or not to stain with intravenous trypan blue appear to be related to the absence or presence of the periodic-acid-Schiff-reactive ground substance of the central nervous system.

Inflammatory or necrotizing injuries of the central nervous system cause a breakdown of the blood-brain barrier, enabling the brain to be stained by trypan blue, administered intravenously or intraperitoneally (King,[10] 1939). Macklin and Macklin[12] (1920) produced stab wounds in the brains of rats and followed the histological changes after intraperitoneal injection of trypan blue. In the present study, similar stab wounds were made and the periodic acid-Schiff technique was applied to see if the effects of the wound caused the reactive substance to disappear at the time of the breakdown of the blood-brain barrier, as defined by the success of trypan-blue staining.

MATERIAL AND METHOD

Stab wounds were made in the brains of 12 adult rats. The animals were anesthetized with

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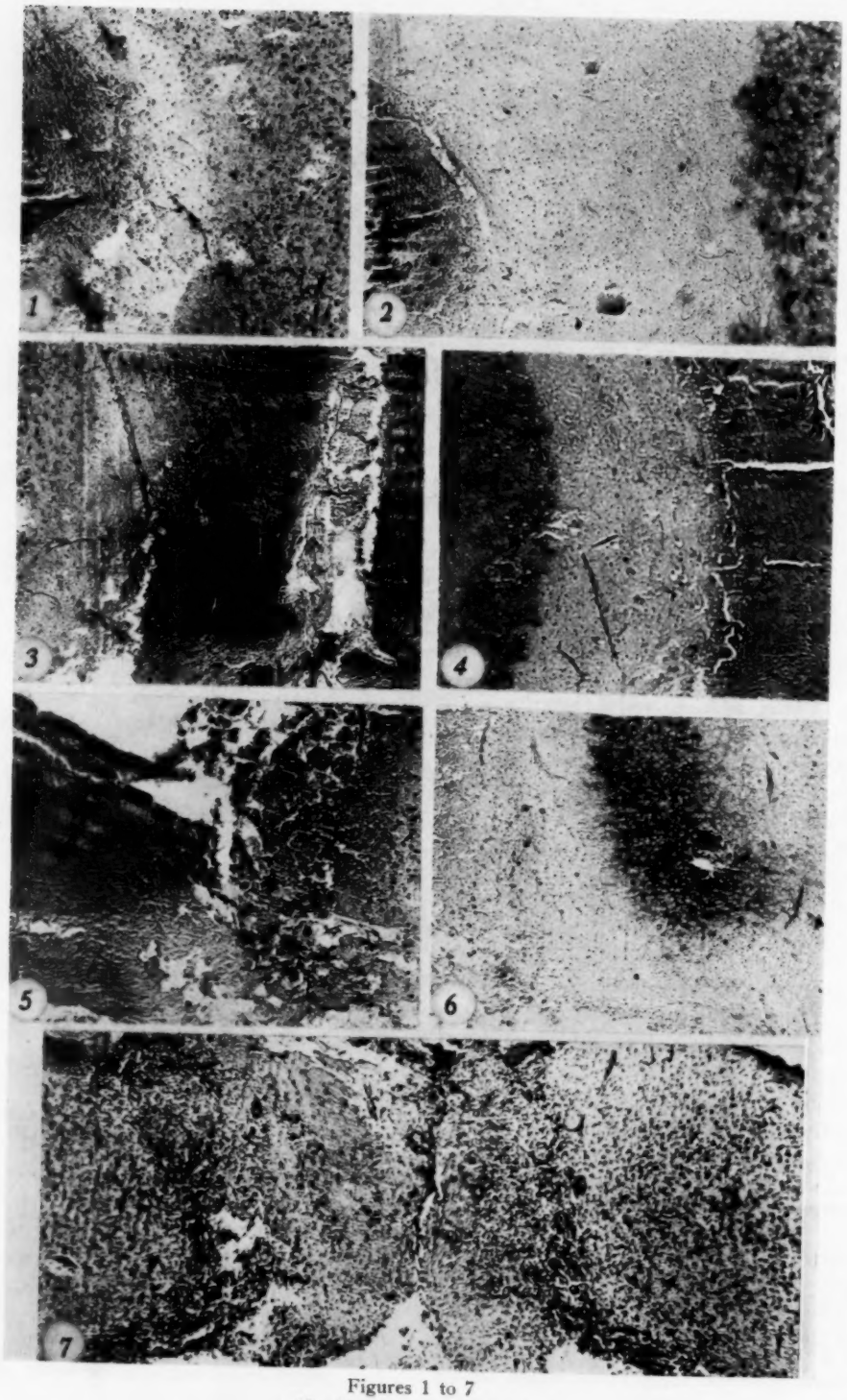
* Penta,[14] cited by King.[10]



Figures 1 to 7

(See legends on opposite page)

ether. The hair was shaved and an incision made through the skin of the head. The muscle and periosteum overlying the skull in the midparietal region were scraped off and a small hole bored in the skull with a dental drill. A dissecting needle, heated in a flame, was inserted through the hole and through the dura mater into the brain to a depth of ¼ to ½ in. The needle was removed quickly, the hole in the skull covered with celloidin, and the skin closed with wound clips. Aseptic technique was not strictly followed, although the instruments used were clean and treated with acetone before use. Subsequent infections were noticed in only 2 of the 12 animals used. However, all of the animals lived and appeared healthy until the time of autopsy.

Animals with brain wounds were killed from 1½ hours to 30 days after the operation. The brains were removed, and a large piece of the brain containing the wound area was fixed in Rossmann's fluid (absolute alcohol saturated with trinitrophenol N.F., 90 ml.; 40% formaldehyde, 10 ml.). Cross and longitudinal serial paraffin sections, 15μ in thickness, of the stab-wound area were made. The slides were stained by the periodic acid-Schiff (PAS) method, as previously described (Hess,[5] 1953) and with hematoxylin and eosin.

RESULTS

Normal brains, subjected to the PAS procedure, stain only in the region of gray matter. The nerve cells and their processes are unstained and are embedded in a pink-staining, PAS-positive matrix, considered to be the ground substance of the central nervous system. In this study, reference to PAS-positive or PAS-negative staining indicates that this matrix substance did or did not stain. The neurons of the higher centers are never stained by this procedure.

The wounds usually extended through the cerebral cortex, cornu Ammonis, and the dorsolateral portion of the middle third of the diencephalon, most commonly injuring the posterior nucleus and the lateral geniculate body of the thalamus. Some wounds passed to the superior colliculus; others more anteriorly, through the anterior nuclear group. Two animals had relatively limited wounds, with the needle passing through only the cerebral cortex and the cornu Ammonis in one, and the other presenting a lesion only of the cortex and subjacent white mattter. Macklin and Macklin[12] have described the detailed changes induced in the brain by stab wounds in sections stained by hematoxylin and eosin. The description herein will be restricted to points that serve the present interest. The results will be confined to a description of the lesion in the cerebral cortex for the most part.

In the early stages after injury (one and a half to six hours), the brain wounds are characterized by three concentric zones emanating from the point of penetration of the needle and seen best in cross section (Fig. 1). The innermost zone is called the coagulum and is a dense zone that presents a

EXPLANATION OF FIGURES 1 to 7

Figs. 1-15.—All photographs are of longitudinal sections of hot stab wounds in adult rat brains and represent magnifications of × 50, except where otherwise stated.

Fig. 1.—Cross section of wound six hours after injury; hematoxylin and eosin. The wound is at the left. The coagulum, the intermediate zone, and the peripheral zone are shown. See Figure 2.

Fig. 2.—Same animal as in Figure 1. Cross section of wound; periodic acid-Schiff technique. The extensive PAS-negative area around the wound is shown. Note the intensely stained glycogen-containing zone at the right.

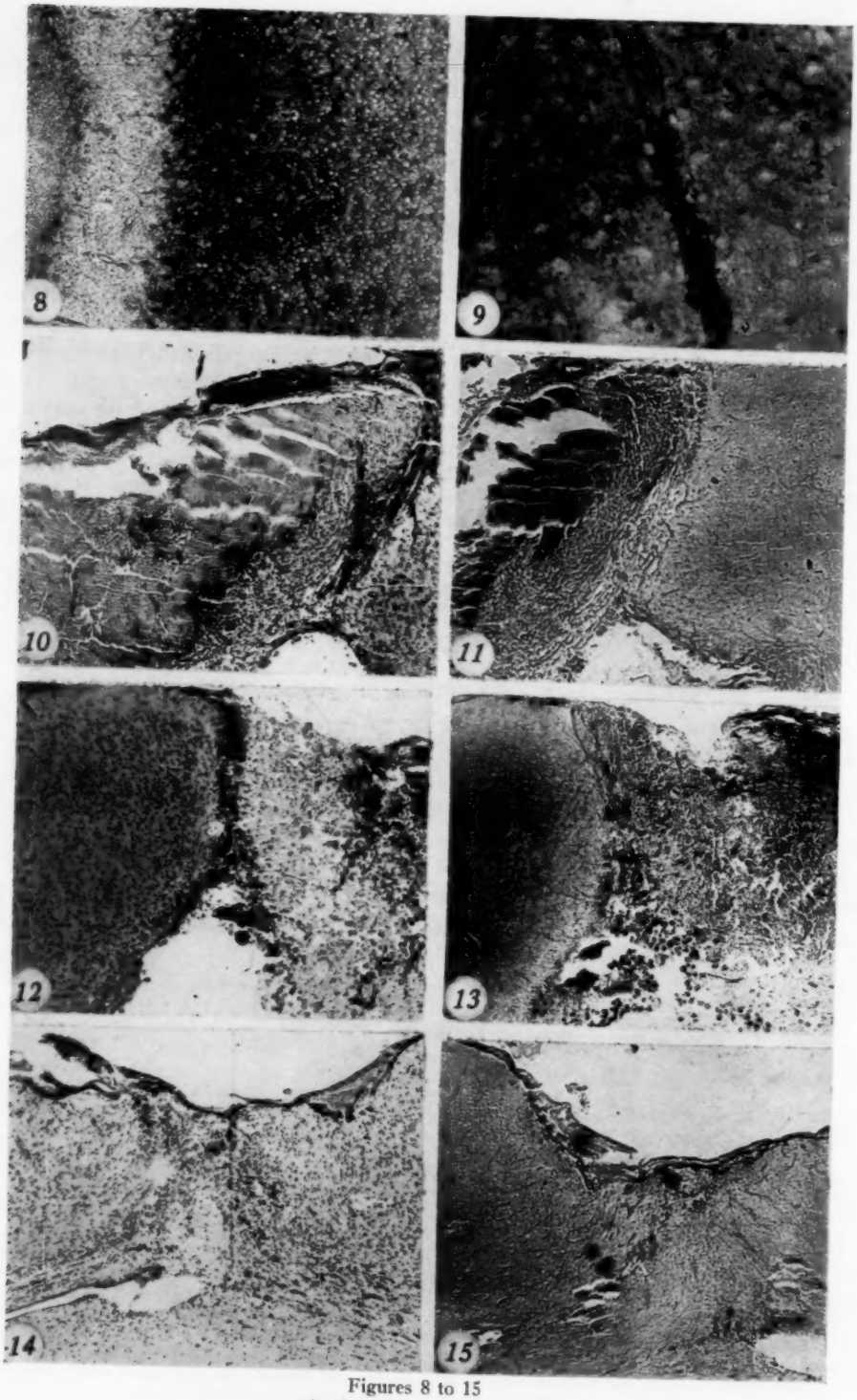
Fig. 3.—One day after injury; hematoxylin and eosin. The wound is at the right. The zones are still evident. See Figure 4.

Fig. 4.—Same animal as in Figure 3; periodic acid-Schiff technique. The extensive PAS-negative area is still present. Note the intensely stained glycogen-containing zone at the left.

Fig. 5.—Three days after injury; hematoxylin and eosin. The wound is at the left. The boundaries between the zones are less evident. Remnants of injured brain are present. See Figure 6.

Fig. 6.—Same animal as in Figure 5. Periodic acid-Schiff technique. The PAS-negative area around the wound is still present, but becoming reduced in extent. Compare with Figures 2 and 4. Note the intensely stained glycogen-containing zone. See Figure 9.

Fig. 7.—Six days after injury; hematoxylin and eosin. The wound is in the center. Macrophages have invaded the wound. The zones around the wound are no longer well defined. A membrane is beginning to form and wall off the injured areas of brain tissue.



Figures 8 to 15

(See legends on opposite page)

ragged inner margin and contains the seared hyperchromatic, pyknotic nerve and glia cells. The next concentric area, named the intermediate zone, is usually relatively lightly stained, and is said by Macklin and Macklin [12] to be produced by the pulling away of the coagulum from surrounding parts. This zone presents a reticulated appearance, with relatively few cells which appear degenerated. Surrounding the intermediate zone is the necrotic wall, consisting of damaged nerve tissue which is not injured as severely as the tissue of the coagulum. This region is sometimes not well defined in sections stained with hematoxylin and eosin. The necrotic wall continues into the peripheral zone, which consists of some injured cells and which grades insensibly into unaffected nerve tissue. PAS staining six hours after injury reveals the coagulum and its ragged border as the most intensely stained area. The intermediate zone, the necrotic wall, and a rather large part of the peripheral zone near the wound do not stain with the PAS method, indicating that the ground substance has disappeared from these areas of injury (Fig. 2).

At one day after injury, the ragged edge of the coagulum has smoothed and stains similarly to the remaining parts of this area. The other zones present essentially no change (Fig. 3). The coagulum stains with the PAS technique. However, again, the intermediate zone, the necrotic wall, and a large portion of the peripheral zone near the lesion are PAS-negative (Fig. 4). Thus, the areas of severe neuronal and glial injury are PAS-negative, with the exception of the coagulum, which consists of debris that probably absorbs the stains and is intensely stained by several histological procedures, and even after intraperitoneal trypan blue administration (Macklin and Macklin [12]).

The zones of the wound are still evident on the third day after the operation. However, the intermediate zone now contains many more cells, since macrophages have wandered into the wound and many lie in this zone. In one animal, the wound was rather severe, and pieces of tissue, disorganized and scattered, remain in the wound area (Fig. 5). An area of the wound, again larger than the intermediate zone itself and extending to regions wherever necrotized nerve cells and neuroglia are found, is PAS-negative (Fig. 6). Thus, the intensely stained coagulum is surrounded by an unstained area, which corresponds to the sites of injury of cellular elements.

The zones are not so well defined at four days after the lesions as previously. The increasing number of macrophages serves to obscure the limits of each zone. By six days, the coagulum and remaining cellular

EXPLANATION OF FIGURES 8 to 15

Fig. 8.—Cross section of wound four days after injury; periodic acid-Schiff technique. The wound is at the left. The PAS-negative area is reduced as compared with that in Figures 2 and 4. Note the intensely stained glycogen-containing zone bordering on the PAS-negative area.

Fig. 9.—Same animal as in Figures 5 and 6; periodic acid-Schiff stain; × 210. The glycogen granules in the glycogen-containing zone are illustrated. Note the accumulation of glycogen around the blood vessels.

Fig. 10.—Ten days after injury; hematoxylin and eosin. The wound is at the left. The membrane at the right surrounding the wounded tissue is well formed and can be seen to extend from the pia-arachnoid.

Fig. 11.—Same animal as Figure 10; periodic acid-Schiff technique. The PAS-negative area around the wound is essentially absent, as is the glycogen-containing zone.

Fig. 12.—Eighteen days after injury; hematoxylin and eosin. The wound is at the right. The injured area is walled off by the membrane. See Figure 13.

Fig. 13.—Same animal as Figure 12; periodic acid-Schiff technique. The PAS-negative area and the glycogen-containing zone are absent.

Fig. 14.—Thirty days after injury; hematoxylin and eosin. The site of the relatively restricted lesion in the center is marked by gliosis. See Figure 15.

Fig. 15.—Same animal as in Figure 14; periodic acid-Schiff technique. No PAS-negative area or glycogen-containing zone is present around the lesion in the center.

debris are crowded with macrophages. Their great number obscures the reticulated appearance of the intermediate zone (Fig. 7). In addition, a membrane, continuous with the pia-arachnoid, is beginning to wall off the lesion. This membrane contains fibroblasts and is reinforced by neuroglia and other wandering cells (Macklin and Macklin [12]). After three days, the PAS-negative areas are not as extensive as before. At four days, the unstained area around the coagulum does not extend so far into the peripheral zone as before; only the peripheral zone adjacent to the necrotic wall is still PAS-negative. This can be seen best in cross sections through the lesion (Fig. 8). The PAS-negative area four days after injury is much reduced (Fig. 8) when compared with that at six hours after operation (Fig. 2). Thus, the ground substance is reappearing; gliosis is present; perhaps some neurons are recovering from the injury.

At 10 days, the membrane appears quite well formed and its extension from the pia-arachnoid can be seen (Fig. 10). The dead tissue appears surrounded by this membrane. Necrotized neurons appear only infrequently outside this membrane, and usually in an area immediately adjacent to it, so that the membrane provides a good standard of separation between the dead and the surviving tissue. The membrane forms a line of demarcation between the PAS-reactive region of dead cells and a narrow zone which is PAS-negative and which lies just outside the membrane (Fig. 11). Still farther outside this narrow zone, the neuropil stains with its customary pink color.

After 10 days, undissolved coagulum and macrophages are still present. The membrane lines the margins of the unaffected regions (Fig. 12). PAS-negative areas are no longer present (Fig. 13). The coagulum is PAS-positive. The unaffected brain also presents a positive reaction to the PAS procedure. This is seen in illustrations of the lesion 18 days after operation.

In an animal allowed to survive for 30 days after the operation the lesions is relatively small, being restricted to the cerebral cortex and underlying white matter. The coagulum has been removed, and the site of the lesion is marked by gliosis (Fig. 14). Some macrophages are also present. PAS-negative regions do not occur (Fig. 15).

Animals with infections were allowed to survive for 11 and 21 days after operation. By this time, both the membrane and invading macrophages have walled off the lesion from the unaffected brain tissue. The brain tissue in these animals, even that portion bordering the lesion and area of infection, is PAS-positive.

In addition, another interesting observation is revealed by a study of brain wounds with the PAS technique. An intensely stained area of the peripheral zone is revealed after wounding and PAS staining. This area is adjacent to the PAS-negative zone surrounding the stab wound and extends for only a short distance into the area of unaffected nerve tissue (Figs. 2, 4, 6, and 8). The darkly stained area is crowded with granules, resembling glycogen (Fig. 9). The granules are no longer revealed after saliva digestion followed by PAS staining, indicating that they are indeed glycogen. A concentration of glycogen is noticed also around blood vessels in this glycogen-containing zone (Fig. 9). Glycogen is not seen in unaffected nerve tissue with the present technique. Glycogen is revealed after the brain stab wound and is present only until about five days after operation. Animals examined six days after wounding and thereafter have only a very attenuated glycogen-containing zone or none at all.

COMMENT

After brain wounds, there is a correlation between the ability of trypan blue to stain the brain, thus testing the adequacy of the blood-brain barrier, and the disappearance of PAS reactivity, which attests an absence or diminution of the ground substance. A similar situation obtains in young animals, where trypan blue can stain the brain easily and extensively; the blood-brain barrier is not yet developed, PAS reactivity has not yet developed, and therefore the ground sub-

stance is not present (Hess,[7] 1955). Therefore, alteration of trypan-blue staining of the brain is accompanied by a modification in the PAS staining of the brain, and the ground substance appears to contribute significantly to the presence of a blood-brain barrier.

The ability of areas of injured brain to store trypan blue can be explained by considering the ground substance as an integral part of the blood-brain barrier. Macklin and Macklin,[12] investigating the appearance of stab wounds of the brain after trypan blue injection, state that the stain, "fairly bright at the one-hour stage, and quite well marked at two and one-half hours, appears at the sixth hour almost as strong as at any later time. . . . The stain remains practically unimpaired until the end of the third day, following which it gradually fades, and by the tenth day is quite weak." After a stab wound of the brain, an extensive area of brain surrounding the wound is PAS-negative. This condition lasts for three days. After three days, the PAS-negative area around the wound begins to diminish in extent. This continues until 10 days after the operation. After 10 days, the PAS-negative area surrounding the stab wound is essentially absent. After such brain wounds, it would seem that the ground substance disappears, begins to be reelaborated starting at the 3d day, and gradually increases in amount, until its regeneration is about complete by the 10th day. Thus, after brain wounds, the breakdown and reconstitution of the blood-brain barrier conform to the same schedule as do the dissolution and reelaboration of the gound substance.

A blow on the head caused only a light staining of the brain by trypan blue (Macklin and Macklin [12]), probably because the ground substance was only diminished slightly in amount and the blood-brain barrier only slightly altered. Similarly, the lack of staining of nerve tissue by trypan blue after retrograde degeneration (King,[8] 1935) can also be explained by assuming that retrograde degeneration is not an injury severe enough to cause disappearance or marked diminution of the ground substance, and consequently of the blood-brain barrier. A similar interpretation can be applied to another experiment by King [9] (1935), involving section of the spinal cord in the lumbar region and the subsequent staining of microglia by trypan blue. At the site of the lesion, vital staining of microglia was most intense. Above the lesion, the microglia stained vitally, though with diminished intensity. In the cervical region, the microglia did not contain trypan blue. Our explanation of these results is that at the lesion the ground substance disappeared, above the lesion the ground substance diminished in amount, and at the cervical level the ground substance was still intact. Hence, the presence or absence of the ground substance seems to be correlated with the presence or absence of the blood-brain barrier, and the consequent absence or presence of trypan-blue staining.

A study of the ground substance in the developing nervous system of the guinea pig gave rise to the suggestion that both neurons and neuroglia, especially astrocytes, are probably the elements responsible for the elaboration and maintenance of the ground substance (Hess [6]). Stab wounds of the brain and severance of the spinal cord cause a degeneration of both neuroglia and nerve cells at the site of the lesion, with a consequent diminution and disappearance of the ground substance. The subsequent neuroglial proliferation is accompanied by a reelaboration of the ground substance. The amount of trypan-blue staining of the brain parallels this sequence of events. Indeed, the observation that astrocytes begin division and increase in number three days after a brain wound (del Rio Hortega and Penfield,[3] 1927; Penfield,[13] 1932) corresponds in time to the beginning of decrease of intensity of trypan-blue staining of brain stab wounds and to the time for the start of reelaboration of the ground substance and reconstitution of the blood-brain barrier after brain stab wounds. Regions of the brain affected by a light blow on the head (Macklin and Macklin [12]), or parts of the central nervous system undergoing retrograde degeneration induced by section

of a cranial nerve (King [8]), or areas distant from a lesion of the spinal cord (King [9]) do not exhibit marked degeneration of glia and subsequent gliosis or complete disappearance of neurons, so that there is no reason to expect any profound effect on the ground substance, or on the blood-brain barrier, or on trypan-blue staining in these areas. A severer retrograde degeneration, such as might be caused by nerve section close to the cells of origin and involving disappearance of nerve cells and gliosis, might perhaps be expected to affect the ground substance and the blood-brain barrier and hence to permit some trypan-blue staining of the affected area of the central nervous system. Similarly, poliomyelitis, depending on its severity, might cause disappearance of some nerve cell bodies and degeneration of glia, a breakdown of the ground substance and the blood-brain barrier, thus enabling trypan blue to stain the brain; indeed, this latter observation was made by MacCurdy and Evans † (1912), who found that trypan blue stained brains infected with experimental poliomyelitis. Thus, to disintegration of ground substance, breakdown of the blood-brain barrier, and ability of intravenous trypan blue to stain the adult brain, we might add lesions of the nervous system severe enough to alter the neurons and neuroglia. Such pathological changes in neurons and neuroglia cause disturbance of the ground substance, and hence disturbance of the blood-brain barrier, which can be shown by the presence of intravenous or intraperitoneal trypan-blue staining of the brain.

At first a concept, then its presence shown (Hess,[5] 1953), the ground substance is probably significant in the development of the nervous system (Hess [6]) and in degeneration and repair of brain wounds, as well as contributing to the constitution of the blood-brain barrier (Hess,[7]) and regulating the penetration of substances into and out of the central nervous system. In addition, a possible significance of the ground substance for neuropathology (edema, cerebral swelling; Hess,[6] 1955) and for the constitution of the synapse (Woollam and Millen,[16] 1954) has also been suggested.

† MacCurdy and Evans,[11] cited by Macklin and Macklin [12] and King.[10]

SUMMARY AND CONCLUSIONS

Stab wounds were made in the brains of adult rats and the brains examined from 1½ hours to 30 days after the operation. The wound areas were stained by the periodic acid-Schiff technique to reveal the effect of the wound on the ground substance. After a stab wound of the brain, an extensive area of brain surrounding the wound is PAS-negative. This condition lasts three days. After three days, the PAS-negative area around the wound begins to diminish in extent. This continues until 10 days after the operation. After 10 days, the PAS-negative area surrounding the stab wound is essentially absent. After such brain wounds, it would seem, therefore, that the ground substance disappears, begins to be reelaborated, starting at the 3d day, and gradually increases in amount, until its regeneration is about complete by the 10th day. This schedule of dissolution and reappearance of the ground substance after brain stab wounds parallels the breakdown and reconstitution of the blood-brain barrier and the ability of wounded brains to stain with trypan blue. Normal brains resist vital staining with intravenous or intraperitoneal trypan blue because of the presence of the blood-brain barrier. Stab wounds cause a breakdown of the blood-brain barrier and permit vital staining. Therefore, the presence or absence of the blood-brain barrier, as revealed by the absence or presence of trypan-blue staining, appears to be related to the presence or absence of the ground substance of the central nervous system. It is concluded that the ground substance of the central nervous system contributes to the constitution of the blood-brain barrier and is the substance that causes normal adult brains to resist vital staining by intravenous or intraperitoneal trypan blue. In addition, it is suggested that the nerve cells and neuroglia elaborate and maintain the ground substance, and that the proliferation of glia and possible recovery of some of the neurons in the above experi-

ments result in the reelaboration of the ground substance. Lesions severe enough to affect adversely neurons and glia will also cause concomitant adverse effects on the ground substance of the central nervous system.

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Chlorpromazine (Thorazine) Treatment of Disturbed Epileptic Patients

Preliminary Report

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This report covers the treatment of 78 epileptic patients at Craig Colony for a period varying from 30 to 60 days. All of the patients were female, and the group under treatment for the longest period represented the worst, most actively disturbed patients in an institution of 2300 patients. The patients were selected in consultation with the ward physician, ward supervisor, and other ward personnel, and the method of selection was simply, "Name your 50 most troublesome patients." All of these patients lived in a closed service and were allowed to continue their daily activities as before. Later, additional cases were added. All were kept under close observation, and laboratory studies were undertaken when indicated by clinical judgment.

Behavior difficulties were characterized by episodic disturbed states and chronic disturbed states, involving hyperactivity, aggression, hostility, assaultiveness, noisiness, resistiveness, temper outbursts, furor states, and destructiveness. Many frequently required large doses of sedation or some form of restraint or seclusion. The majority had shown varying degrees of deterioration. With the exception of 3 patients, all were mentally defective, with 12 in the idiot group, 22 in the imbecile group, 25 in the moron group, and 16 borderline.

Mental Status		Age Groups, Yr.	
Idiot	12	12-15	7
Imbecile	22	16-20	10
Moron	25	21-29	21
Borderline	16	30-39	19
Normal	3	40-49	12
		50-59	7
		60 +	2

Some of the patients were frankly psychotic. Twenty-eight of these patients were inaccessible by reason of mutism, mental defectiveness, and/or deterioration. Fifty-one were classified under idiopathic epilepsy and 27 under symptomatic epilepsy.

Idiopathic	51
Symptomatic	27
Agenesis and birth injuries	9
Meningoencephalitis	9
Metabolic defects	2
Postnatal trauma	6
Endocrinopathy	1

The ages of the patients varied from 12 to 61 years. Twelve patients had been afflicted with epilepsy for periods of 4 to 9 years; the others had suffered epilepsy for periods varying from 10 to 52 years, with an average of over 26 years. Five patients have been in the institution less than 6 months; 25, from 1 to 9 years, and 48, from 10 to 29 years, with an average institutionalization of approximately 17 years.

ADMINISTRATION AND DOSAGE

Chlorpromazine was administered orally to all patients except six, who received it parenterally when they refused oral medication during acute excitement states. It was never necessary to give more than two successive parenteral injections, as the excitement states were fully controlled and the patients willing to take oral therapy. Parenteral chlorpromazine was given in 100 mg. doses, with 50 mg. given intramuscularly in each buttock. How-

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ever, to control any possible discomfort, 1 cc. of 2% procaine was added to each 50 mg., the drug injected rapidly, and the area of injection massaged. No special precautions were taken to compel the patient to lie down.

The oral dose varied initially from 200 to 300 mg., with almost two-thirds of the patients receiving 300 mg. daily. These doses were maintained, decreased, or increased as clinical judgment indicated. All except one received a barbiturate singly or in combination with other anticonvulsants.

The 78 patients under therapy were separated into three equal groups. The first group had no reduction of phenobarbital, and their average daily intake was 4½ grains (0.28 gm.). In the second group, each patient's phenobarbital dose was reduced one-third, and 12 patients had an additional reduction of barbital sodium, varying from 2½ to 10 grains (0.15 to 0.6 gm.), average 6.7 grains (0.4 gm.). The intake of phenobarbital in this group averaged 2.92 grains (0.175 gm.). In the third group, phenobarbital was reduced 50%, and 17 patients had a further reduction of barbital sodium of 2½ to 20 grains (0.15 to 1.2 gm.), average 8.9 grains (0.534 gm.). The daily phenobarbital intake averaged 1.81 grains (0.108 gm.).

PURPOSE OF RESEARCH

Three questions were of paramount interest in this study:

1. Was chlorpromazine of any value in controlling episodic and chronically disturbed epileptics?

2. What effect would it have on convulsions?

3. Was there any intensification of barbiturates, and to what degree?

In evaluating the use of chlorpromazine in epilepsy, it is well to emphasize, at this time, three facts that are axiomatic with epileptics. First, they are subject to varying periods of remissions from seizures; second, they are subject to exacerbations of seizures, and, finally, they run the hazard of status epilepticus and/or serial seizures whenever there is an abrupt reduction or withdrawal of any anticonvulsant. Many of these patients had their epilepsy fairly well controlled, but since their psychomotor disturbances, excitements, and furor states constituted a problem of serious magnitude, the hope and promise of a new therapy to ameliorate these states was worth any risk that could be potentially involved. However, the risk was minimized by close supervision on closed wards.

RESULTS

Acute Excitement States

The parenteral injection of 100 mg. of chlorpromazine was rapid and highly effective in the acute excitement states, quieting and relaxing the noisy, hyperactive, resistive patients within 30 to 45 minutes. While this series of six patients is small, chlorpromazine proved to be a very effective therapeutic agent and is far superior to scopolamine, apomorphine, and the various barbiturates previously used in treatment.

Chronic Disturbed States

The behavioral response in the chronic disturbed states was also exceedingly gratifying. The patients exhibited considerable less irritability, hostility, aggression, and assaultiveness. Noise subsided appreciably. They became quieter, more relaxed, and more cooperative, and those whose deterioration or mental defect was not pronounced became interested and participated in ward activities. Anxiety and tension states were reduced—patients volunteered statements such as, "I lost my temper," "I can control my temper better," or "I don't feel as nervous as I did." There were fewer outbursts of temper, and, when present, the outbursts were less intense and of shorter duration than those previously shown. Restraint and seclusion were minimal. There was less destruction to clothing, linen, and windowpanes. The administration of parenteral and oral sedation was markedly reduced. Appetites increased in the majority, with 56 patients showing a weight gain of 1 to 21 lb.; 23 gained 1 to 5 lb.; 17 gained 6 to 10 lb.; 10 gained 10 to 14 lb.; 4 gained 15 to 19 lb., and 2 gained 21 lb. Thirteen lost 1 to 5 lb.; 3 lost 6½ lb., and 6 had no change in weight.

The behavioral response was markedly improved in 32, or 41%; moderately improved in 20, or 25.6%; slightly improved in 13, or 16.7%, and unimproved in 13, or 16.7%. The results were essentially identical in all groups in the total number of patients responding favorably to chlorpromazine.

The behavioral response in relation to reduction in phenobarbital intake was as follows:

Behavior	No Reduction	33.3% Reduction	50% Reduction
Markedly improved.....	8	10	14
Moderately improved.....	9	8	3
Slightly improved.....	3	5	4
Unimproved	6	3	5

Significant improvement was evident in all age groups.

Ages	Totals	Markedly Improved	Moderately Improved	Slightly Improved	Unimproved
12-15	7	4	2	..	1
16-20	10	2	3	2	3
21-29	21	9	4	1	7
30-39	19	12	3	3	1
40-49	12	4	4	4	..
50-59	7	1	4	2	..
60-61	2	..	..	1	1
Totals	78	32	20	13	13

A few illustrations of patients markedly improved follow.

A. M., a 13-year-old girl of normal mentality (I. Q. 103), had been an epileptic with uncinate fits since 5½ years of age. She has been in the institution over two years. Epilepsy was minimal (two grand mal and two petit mal seizures since admission), but her behavior was a major problem because of hyperactivity, aggressiveness, irritability, and extreme emotional instability, with almost daily explosive temper outbursts. Stuttering was prominent, but worse during excitements. Restraint and seclusion was no novel experience, and she was classified to a closed service. Chlorpromazine was begun at 300 mg. and currently is maintained at 150 mg. daily. Phenobarbital was reduced 50%. Improvement has been dramatic from the first day. She has become quiet, cooperative, and productive. There has been no explosive outburst. Full ground privileges have been restored. This patient's release from the institution at this time is precluded by reason of her status as a deportable alien.

C. S., a 31-year-old patient, an uncommunicative idiot, has been an epileptic for 28 years and has lived at the institution for the past 25 years. Her epilepsy has been well controlled in recent years, but she has been chronically disturbed for many, many years, her behavior being characterized by guttural noises day and night. Heavy sedation was prescribed frequently, with little or no effect. She quieted almost immediately with chlorpromazine, has required no further sedation, and is maintaining her improvement on a daily maintenance dose of 50 mg.

R. B., a 24-year-old epileptic of moron intelligence, has lived at the institution for the past 15 years. Epilepsy has been present since birth and quite severe until the past year. Periodically, she has had severe temper outbursts, has been noisy, hyperactive, and aggressive, particularly at the time of her menses, and has required frequent sedation and restraint. These episodes had become so intense in frequency and duration that she had to be kept on a closed service. Except for a minor momentary outburst of anger with a provocative patient, there has been no rage reaction either at her menses or at any other time.

M. D., a 30-year-old imbecile, has been an epileptic for 27 years and has resided in the institution for 24 years. Her epilepsy has been well controlled, only one grand mal and two petit mal attacks having been observed since January, 1950. She has been chronically disturbed for many years, her behavior being characterized by yelling in a deep, hoarse, masculine voice, obscenity, aggression, resistiveness, hyperactivity, and destructiveness. Under treatment she has made excellent progress and has become quiet, pleasant, cooperative, and productive in ward activities, and her voice has lost its hoarseness and masculine quality.

Effect on Seizures and Intensification of Barbiturates

Patients in the first group, the majority of whom were under treatment for 30 days, received an average of 4½ grains of phenobarbital daily. Only two patients (S. J. and S. S.) could possibly be considered as having shown an increase in seizures; for example, S. J. had four grand mal seizures within 30 days after treatment, whereas no seizure had been observed during the previous 14 months. S. S. had a grand mal seizure on the 22d day after treatment, whereas none had been observed during the previous 15 months. Five patients had no seizures for 30 days, while four other patients had no seizures for 60 days. However, one of the patients without seizures did develop a coma, and this will be mentioned later.

The second group, which had a 33.3% reduction in barbiturates, has been under observation for 60 days. In this group, 4 patients had no seizures, 11 had no apparent change in seizure frequency, and 11 patients showed an appreciable alteration of their previous seizure frequency. Of the last group, four (M. B., R. M. G., S. H., M. A. R.) had a marked increase in seizure frequency for varying periods up to 12 days; four (R. B., M. D., C. K., M. R.) had a

moderate increase, and three (S. K., B. L., F. S.) had a questionable increase. Seizure control was completely reestablished in six (M. B., M. A. R., M. R., R. B., M. D., S. K.) upon restoring the previous phenobarbital dosage.

The third group, with a 50% reduction in barbiturates, was also under observation for 60 days. Four patients had no seizures; seven patients had no change in seizure frequency; six patients had a questionable increase (A. M., E. R., C. S., M. I. D., S. S., M. McG.); four (E. N., Y. G., A. McG., M. S.), a moderate increase, and five (G. B., C. C., L. M. D., M. McQ., E. B.), a marked increase.

	No Reduction	Reduced 33⅓%	Reduced 50%	Total
No seizures	9	4	4	17
No change	15	11	7	33
Questionable increase	2	3	6	11
Moderate increase	..	4	4	8
Marked increase	..	4	5	9

The results for these three groups show that 17 patients developed no seizures and 33 had no essential alteration of previous seizure frequency, whereas 11 patients showed a questionable increase, and 17 patients a moderate to marked increase, in their seizure frequencies. It is highly significant that 26 of the 28 patients who showed any questionable or appreciable increase in their seizure frequencies were in the groups in which barbiturates were reduced one-third or one-half, thus strongly indicating that the seizure increase was due essentially and specifically to the reduction of phenobarbital rather than to any action of chlorpromazine.

For example, M. A. R. had 40 grand mal and 4 petit mal seizures in 1954 and none in 1955 before treatment, but during the first eight days after chlorpromazine was started and barbiturates reduced she had 27 grand mal seizures. Since restoration of phenobarbital no seizure has occurred. M. B., a patient who had an inadvertent reduction of diphenylhydantoin (Dilantin), in addition to the barbiturate, developed seizures daily for 13 consecutive days, totaling 37 grand mal and 5 petit mal, whereas she had 38 grand mal and 10 petit mal seizures in 1954 and none the three weeks prior to chlorpromazine. Seizures were abruptly controlled with restoration of the previous dose of phenobarbital and diphenylhydantoin. Where seizures became aggravated, seizure control in most instances was easily reestablished by returning to the prechlorpromazine level of phenobarbital except in one patient (G. B.), who died. On the other hand, a few patients stabilized themselves after demonstrating a seizure increase for seven days without recourse to additional phenobarbital.

In the single death, it is, at best, difficult to evaluate the role of chlorpromazine, but here the drug is suspect of precipitating serial seizures or status epilepticus. However, it again should be emphasized that a similar picture can and does frequently occur in epileptics not under treatment with chlorpromazine. The death (G. B.) occurred in a 29-year-old mute of idiot mentality who had been an epileptic since 4 months of age and who had spent the last 17½ years of her life within the institution. She had been chronically disturbed for many years, was resistive, aggressive, noisy, and destructive, and frequently required heavy doses of sedation and/or frequent restraint or seclusion. Her seizures had been very well controlled for the previous four years, only three grand mal and three petit mal attacks having been observed since January, 1951. From 1937 to 1951 she averaged 24 grand mal seizures annually and had never exceeded more than 2 grand mal seizures in any one day. The barbiturate medication prior to treatment consisted of 4½ grains of phenobarbital and 10 grains of barbital sodium daily. This was reduced to 2¼ grains of phenobarbital daily. The chlorpromazine dosage started at 200 mg. and reached a maximal dose of 600 mg. The patient had been under therapy for 41 days when the first grand mal seizure occurred. This, incidentally, was 48 hours after the maximal dose had been reached. This was followed by two grand mal attacks on the 42d day, a single grand mal seizure on the 43d day and

eight grand mal seizures on the 44th day. On the 44th day the drug was discontinued, with the beginning of serial seizures. Fifty-two grand mal seizures developed within the next 31 hours, and the patient died of pulmonary edema on the 46th day of treatment.

Intensification or potentiation of barbiturate is again a difficult question to evaluate, but if marked drowsiness and incoordination can be used as a qualitative gauge, then only 5 of the 78 patients were so affected and 1 of these became comatose. This occurred in a 21-year-old mute patient (M. A.) of idiot mentality who was placed under treatment because of hyperactivity, destructiveness, self-mutilation, and noisiness. She had been an epileptic since birth and had lived within the institution for 16½ years, averaging one grand mal seizure annually for the five previous years. The daily dose of phenobarbital was 4½ grains when she was placed on chlorpromazine therapy. The dosage began at 100 mg. daily and was gradually increased to 400 mg. She had been under treatment for 47 consecutive days and had experienced no seizures. One week after her maximal dose she became deeply comatose, with a weak and slow pulse, slow and shallow respiration, and initial blood pressure of 82/68. She remained in coma for two days before reacting. No seizures had occurred during chlorpromazine therapy. In this single coma and in the four other cases of severe drowsiness, chlorpromazine undoubtedly was a contributory factor, but an element of doubt is raised as to whether these side-reactions are due to an intensification of the barbiturate or to an individual idiosyncrasy or intolerance of the patient for chlorpromazine or to a combination of the two.

Complications

A slight to moderate fever developed in 11 patients and was usually present between the 7th and the 10th day. Fever was invariably associated with constipation and subsided within 3 to 24 hours after adequate elimination. The ward personnel reported that patients under chlorpromazine therapy were more constipated and required more cathartics and enemas than before. Five patients (M. I. D., M. G., H. F., F. S., L. D.) developed a macular or maculopapular rash, which was irregularly distributed except in a single case, in which it was generalized and symmetrical. One patient (L. D.) developed an intermittent fever and rash and finally had to be dropped from therapy. Coarse tremors of the upper extremities were present in five patients; drooling, in four, and ringing of the ears, in two. Two patients (C. S. and B. L.) developed jaundice and clay-colored stools, and both conditions cleared up within six days after discontinuing the drug. Eosinophilia (13% and 22%) was noted in two cases. The previously reported coma and death complete the list of complications. The coma and death and the jaundice in one case occurred in patients receiving daily doses of 400 to 600 mg.

Summary and Conclusions

The period of observation is admittedly quite short and the series small, but the results so far observed among the most disturbed epileptics in the institution indicate the following conclusions:

1. Chlorpromazine (Thorazine) has been highly effective and dramatic in controlling behavior disturbances.

2. The drug can be safely administered with fairly large doses of phenobarbital with minimal risk.

3. Doses of 300 mg. or less are less likely to be involved in complications.

4. A maintenance dose may be necessary to retain control of both episodic and chronic disturbed states.

5. Chlorpromazine does not appreciably reduce the frequency of seizures when maintenance therapy of phenobarbital or diphenylhydantoin (Dilantin) is reduced.

Smith, Kline & French Laboratories, the manufacturer of Thorazine, furnished the drug for part of this study.

Meningiomas of the Posterior Fossa

Their Diagnosis, Clinical Features, and Surgical Treatment

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Meningiomas originating within the posterior fossa frequently cause much difficulty in diagnosis, and there are few intracranial tumors so challenging to the neurosurgeon. Whereas meningiomas in their favored locations, such as the olfactory groove, the sphenoid wing, the convexity, and the parasagittal region, give rise to characteristic clinical features, those within the posterior fossa differ widely in their mode of onset and the symptoms they produce. In some cases the development of symptoms may be so insidious and misleading that posterior fossa tumors seem remote from consideration. In other instances the histories and neurological findings are indistinguishable from those of an acoustic neurinoma. Since meningiomas in general offer a favorable prognosis, early diagnosis of the ones within the posterior fossa is particularly important because of their propensity to involve vital structures in or about the brain stem.

The incidence of subtentorial meningiomas has been very low. As recently as 1953, Russell and Bucy [5] were able to collect only 120 surgical cases from the literature, adding 12 of their own. But it is probable that the incidence will increase as the nature of these tumors is better appreciated, and that with earlier diagnosis the operative mortality will decrease. The literature on meningiomas of the posterior fossa is quite meager, and up to 1954 there have been only five reported case series of significant numbers: 1938, Cushing and Eisenhardt,[3] 24 cases (23 were surgical); 1948, Campbell and Whitfield,[1] 9 cases; 1950, d'Errico,[4] 10 cases; 1953, Russell and Bucy,[5] 15 cases (12 were surgical), and 1953, Olivecrona,[2] 71 cases (70 were surgical).

It would seem worth while, therefore, to record the results of 20 years' experience with this subject and to further its more widespread interest.

MATERIAL

The present series is composed of 29 cases of meningioma originating within the posterior fossa and treated surgically at the Lahey Clinic during the 20-year period from Jan. 1, 1934, to Jan. 1, 1954. During the first 10-year period there were 16 cases, and in the second 10-year period, 13 cases.

SYMPTOMATOLOGY

There was a definite relationship to age in this series, with almost 50% of the patients ranging between 45 and 60 years; the youngest was 15 years, the oldest 72 years. The average age at the time of operation was about 45 years. These figures compare closely with those of Russell and Bucy, in 136 cases.

Of the 29 patients, 23 were women and 6 were men. This finding differs considerably from the sex ratio of 7:3 (women to men) in the 136 cases reviewed by the above authors.

Clinical histories varied greatly. In one case the previous diagnosis had been senile psychosis due to arteriosclerosis (Case 25).

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TABLE 1.—*Neurological Symptoms*

	No.
Headache	22
Unsteadiness	18
Tinnitus	12
Loss of hearing	12
Nausea	10
Vomiting	10
Dizziness	10
Difficulty in swallowing	7
Motor weakness (arm or leg or both)	6
Blurring or visual failure	5
Diplopia	4
Facial paresthesias or numbness	4
Mental symptoms	4
Facial palsy	2
Dysarthria	2
Paresthesias of extremities	2
Retro-orbital pain	2
Loss of taste	1
Loss of smell	1

Another patient had been in a mental institution before the possibility of tumor was considered (Case 1). Spinal cord tumor was strongly suspected in another (Case 4), while multiple sclerosis had been diagnosed repeatedly in one patient (Case 29). Postpartum psychosis dominated the differential diagnosis in another (Case 19). The history most commonly simulated, however, was that of the cerebellopontine-angle or acoustic neurinoma. The longest duration of symptoms before surgical intervention was 11 years (Case 9), and the briefest interval from onset to operation was 5 weeks (Case 19). The average duration of symptoms of all cases was 3.6 years.

Headache was the symptom most frequently encountered (22 cases, or 76%). In many instances, however, headache was of secondary importance to the patient or was a late symptom, due to increased intracranial pressure. Our experience with this symptom, therefore, does not agree with that of d'Errico, who emphasized headache as one of the first and most constant symptoms. Certain types of headache appear to be related specifically to these tumors. Dull, aching pains in the occipital, occiptomastoid, and occipitocervical regions, when present, were considered suspicious. In these cases stiffness or tenderness of the neck muscles was usually present.

Unsteadiness was next in order of frequency (18 cases, or 62%). In some it was related to sudden changes in posture, while in others there was evidence of definite staggering. Some patients noted a tendency to deviate to one side when walking. Unsteadiness often developed late in the clinical course, a finding which has been noted by others. Tinnitus, loss of hearing, nausea, vomiting, and vertigo occurred with almost equal frequency (40%), while only four patients complained of diplopia. In Table 1 the neurological symptoms encountered and the number of instances of each are listed.

It should be mentioned that nausea and vomiting were not always late symptoms or manifestations of increased intracranial pressure. In a few patients nausea and vomiting occurred early in the clinical course. The frequent involvement of the vagus nerve by the tumor may be the explanation for these symptoms.

NEUROLOGICAL FINDINGS

Cerebellar signs were present more frequently than not, but in many instances were not prominent. Incoordination of movement in some form (ataxia of gait, incoordination of extremities, or dysdiadokokinesis) was present in 22 cases (76%). Nystagmus was observed in 19 cases (65%). In all of these nystagmus was of the horizontal type, but in four cases a vertical component was also present. As a lateralizing sign, nystagmus was not consistently reliable, although often it was coarser on gazing to the ipsilateral

TABLE 2.—*Cranial Nerve Signs*

		No.
Impairment of hearing		15
Partial	5	
Complete	10	
Hypalgesia and hypesthesia of face		13
Absent or decreased corneal reflex		11
Facial weakness		8
Abducens weakness		4
Laryngeal palsy		2
Sternocleidomastoid weakness or atrophy		2
Hypoglossal weakness		2
Absent gag reflex		1
Anosmia		1
Optic atrophy		1
Ptosis		1

side. Hypotonia was detected in only four cases of the series.

Cranial nerve palsies were conspicuous, and the acoustic nerve was foremost in frequency. Hearing loss on the affected side was found in 15 patients (52%). In 10 of these hearing loss was complete, and in 5 it was partial. Data regarding caloric responses were insufficient for analysis. Trigeminal root involvement was next in order of frequency. In 13 patients (45%) there was ipsilateral hypesthesia or hypalgesia of one or more divisions (rarely all three), while the corneal reflex was decreased or absent in 11 cases. In Table 2 the cranial nerve signs and the number of instances are listed.

Papilledema was present in 15 patients. In the majority of these (12 cases) it was bilateral, with little or no difference between the two sides. When there was a difference, it was found to have no significance in regard to the side of the lesion.

Long-tract signs were relatively uncommon. Hyperreflexia was found in 11 patients (38%) and was usually symmetrical in distribution. Three patients showed a hemiparesis, and two others, one of whom was practically paraplegic, had weakness of all four extremities. Sensory disturbances were infrequent and of variable extent except in one case, in which there was a sensory level at the second cervical segment (Case 4). Horner's syndrome was noted in one case.

SPINAL FLUID

Lumbar puncture was performed in 10 instances. The pressures ranged from 120 to 340 mm. but in the majority of cases were between 150 and 205 mm. Spinal fluid protein, in most cases, was normal or but slightly elevated. In only two patients was the protein level above 100 mg. (125 and 1900 mg.). In the second case there was a block just below the foramen magnum (Case 4). Thus, the spinal fluid protein level in meningiomas of the posterior fossa is important in distinguishing them from acoustic neurinomas.

ROENTGENOLOGIC FINDINGS

Reports of routine roentgenograms of the skull were available in 24 patients. In 13 of these (54%) there were no significant abnormalities. In the remainder, definite roentgenologic signs were present. Five disclosed erosion or thinning of the internal auditory meatus or medial end of the petrous ridge. In three cases there were dense calcifications in the posterior fossa. Negative skull roentgenograms appeared to be of little value in excluding these tumors.

TABLE 3.—*Sites of Attachment*

		No.
Internal auditory meatus		8
Lateral sinus		6
	Transverse portion	3
	Sigmoid portion	2
	Jugular foramen	1
Base of posterior fossa		4
	Basisphenoid	2
	Lateral floor	1
	Foramen magnum	1
Petrosal sinus and posterior surface of petrous bone		4
Tentorium		6
	Incisura	3
	Inferior surface	2
	Dumb-bell tumor (above and below)	1
Torcular Herophili		1
Total		29

VENTRICULOGRAPHY

In the majority of our cases the history and neurological findings were sufficiently definite to indicate the need for surgical intervention and the anatomical approach of choice. In 13 cases, however, ventriculography was performed. In six of these the ventriculogram disclosed no lateralizing findings, there being a dilatation of the lateral and third ventricles with nonfilling of the fourth ventricle. In five cases the fourth ventricle was partially demonstrated and was displaced from its anatomical position, so that more precise localization was possible before operation. In two patients the ventriculographic findings were compatible with occipital or parieto-occipital tumor (Cases 3 and 17).

PATHOLOGY

In all cases the tumor was verified at operation and partial or complete removal performed. The majority were typical meningiotheliomatous meningiomas. Only one was of the psammomatous type, and another was described as an hemangiomeningioma. The most frequent site of origin was the region of the internal auditory meatus (eight patients, or 28%). This corresponds very closely with Cushing's series, in which 7 of 24 patients with meningiomas of the posterior fossa presented an acoustic syndrome. The sites of attachment are shown in Table 3.

SURGICAL APPROACH

The preoperative differentiation of meningioma of the cerebellopontine angle and acoustic neurinoma is of no great practical value from a surgical standpoint. In such cases the standard unilateral suboccipital craniectomy provides adequate exposure. The problem of supratentorial extension of the tumor has seldom been difficult, and it has usually been possible to deal with this situation by dividing the tentorium and removing the supratentorial portion from below. Extensions of the tumor above the tentorium actually occurred in eight cases. In five of these it was possible to attack the supratentorial portion from below. In one case (Case 13), however, an occipital approach was used when the tumor arose from the internal auditory meatus. It extended forward to the anterior clinoid process and caudally into the spinal canal as far as the second cervical segment.

When there is evidence that the site of attachment is the tentorium with involvement of the anterosuperior surface of the cerebellum, an occipital flap provides the most feasible approach (Cases 17 and 18). In many instances a full suboccipital craniectomy affords adequate exposure. Multiple-stage procedures, recommended by some neurosurgeons, have been necessary in only five patients. In one of these, at the first stage nothing more than a suboccipital decompression was attempted. In the second stage a complete removal was accomplished.

The technical removal of these tumors is often extremely difficult, owing to their excessive vascularity and their great adherence to many cranial nerves. The basilar artery is often displaced or surrounded by tumor, and at times one or both vertebral arteries may be involved. Pressure indentation of the pons and medulla is common, so that separation of the capsule from these structures is most hazardous, if possible at all. Since the base of the tumor is frequently attached to one or more of the large dural sinuses, removal of this portion is often a difficult feat. Yet every attempt consistent with safety and good judgment should be made to remove the tumor completely at the first procedure. Not only does this spare the patient subsequent operations, but if much time elapses between stages, there is more probability of extension into critical regions anterior to the brain stem.

TABLE 4.—*Mortality for Six Series*

	Cases	Per Cent
Cushing	24	8
Campbell and Whitfield	9	33
d'Errico	10	20
Russell and Buey	12	50
Oliverona	71	31
Horrax and Poppen	29	24

In 22 cases (76%) complete removal of tumor and capsule was accomplished. In four of these the procedure was done in two stages (excluding Case 8, which was a recurrence after an interval of eight years). In seven cases complete removal could not be accomplished.

The immediate postoperative mortality in this series was 24%. In the first 10-year period (16 cases) the mortality was 31.2%, while in the second 10-year period (13 cases) the mortality was 15.4%. This mortality is compared with that of other case series (Table 4).

It is important to note that in Cushing's series, though there were only two operative

TABLE 5.—*Summary of Cases*

Case	Age and Sex	Predominant Symptoms	Signs	Attachment of Tumor	Operation	Result	Useful Survival
1	59 F	Headaches for many years, weakness of all limbs, 6 mo.; mental deterioration, 6 mo.	Papilledema; spastic quadriparesis	Tentorium to incisura	1. Suboccipital decompression. (J.L.P.) 2. Removal (G.H., J.L.P.)	Recovered	14 yr.; died of bronchopneumonia
2	39 F	Vertigo; right-sided deafness and tinnitus, 4 yr.	Papilledema; nystagmus, right; V, VIII *; right cerebellar signs	Posterior petrous bone	Removal (G.H., J.L.P.)	Died 23 days, meningitis	.....
3	49 M	Headaches and failing vision, 4 mo.	Papilledema; nystagmus; right hemiparesis; right homonymous hemianopsia	Tentorium at torcula, left occipital, left and right cerebellar	1. Left occipital craniotomy (G.H., J.L.P.) 2. Right suboccipital craniotomy with completion of removal (J.L.P., G.H.)	Recovered	7 yr.; sudden death, no autopsy
4	56 F	Numbness of fingers and weakness of legs, 2 yr.	Spastic quadriparesis; C 2 sensory level; spinal block at C 1 and C 2	Foramen magnum, extension left cerebellar fossa	1. Suboccipital decompression and cervical laminectomy (G.H., J.L.P.) 2. Removal 1 yr. later	Recovered	16 yr.
5	61 F	Occipital headache and unsteady gait, 3 yr.; deafness, 20 yr.; tinnitus and vertigo, 10 yr.; nausea and vomiting, 6 mo.	Total deafness; nystagmus; ataxia	Lateral sinus, left	Removal (J.L.P.)	Recovered (deafness unrelated)	15 yr.
6	42 F	Speech difficulty, 8 yr.; headaches, 6 yr.; double vision, 4 yr.	Nystagmus; left V-XII; left cerebellar signs	Lateral floor posterior fossa, left	Removal (G.H., J.L.P.)	Died 15 days, bronchopneumonia	
7	53 F	Dizziness, headaches, tinnitus right ear, unsteadiness, 3 yr.; deafness right ear, 2 yr.	Right V, VII, VIII; mild ataxia	Right internal auditory meatus	Removal (G.H., J.L.P.)	Recovered	15 yr.
8	70 F	Recurrence of symptoms following partial removal of cerebellopontine angle meningioma 7 yr. previously (H. Cushing)	Right VII and VIII; nystagmus; marked ataxia	Right internal auditory meatus	Removal (G.H., J.L.P.)	Died 1 day	
9	41 F	Headaches, 11 yr.; 3 episodes of severe headache with nausea and vomiting	Mild dysarthria; ataxia in upper limbs	Sigmoid sinus, right	Removal (G.H., J.L.P.)	Recovered	15 yr.
10	39 F	Headaches, 3 yr.; dizziness, staggering, speech and swallowing difficulty, 3 mo.	Papilledema; nystagmus (horizontal and vertical); mild right VII, IX, XII ataxia	Clivus	1. Partial removal 2. Further partial removal one mo. later	Died 10 days following second procedure	
11	47 F	Episodes right retro-orbital pain, 9 yr.; decreased hearing, tinnitus right ear, progressing to deafness, 3 to 4 yr.; numbness right face and unsteadiness, 2 yr.	Mild papilledema; nystagmus; right V, VII, VIII; Romberg positive; ataxia of gait	Right internal auditory meatus	Subtotal removal (G.H., J.L.P)	Recovered	14½ yr.
12	55 M	Slight unsteadiness, 3 to 4 yr.; emotional lability, 1 yr.; sharp intermittent pains over right eye, 4 mo.	Early papilledema; nystagmus; right cerebellar signs; right hyperreflexia; right Babinski	Tentorium, mainly posterior fossa, extension into middle fossa	Removal (J.L.P., G.H.)	Died 18th day	.....
13	15 F	Failing vision, 2 yr.; diplopia, headache, dysphagia, 1 yr.; staggering gait, 8 mo.	Papilledema; right V-XI; right ataxia	Right internal auditory meatus	1. Subtotal removal (G.H., J.L.P.) 2. Ventriculocisternostomy 10 mo. later	Partial recovery Died 2 mo. after second operation	....
14	38 F	Headaches and dizziness, 2 yr.; loss of hearing and tinnitus, 6 mo.	Papilledema; diminished hearing on left; ataxia	Incisura of tentorium	Removal (J.L.P.)	Poor recovery; persistent mental confusion; died 1 yr. later	.....

TABLE 5.—*Summary of Cases*—Continued

Case	Age and Sex	Predominant Symptoms	Signs	Attachment of Tumor	Operation	Result	Useful Survival
15	42 M	Left suboccipital pain intermittent, 10 yr.; vertigo and unsteadiness 8 mo.	Papilledema; nystagmus; left suboccipital tenderness; ataxia left extremities	Clivus	Subtotal removal (J.L.P.)	Gradual recovery	12 yr.
16	52 F	Headaches and unsteadiness, 18 mo.	Right V; right ataxia	Lateral sinus, right	Removal (G.H.)	Recovered	11 yr.
17	34 M	Frontal headaches, 3 yr.; visual loss and episodic vomiting, 2 yr.	Papilledema; left homonymous hemianopsia; left hyperreflexia; Romberg positive; ataxic gait	Tentorium, right above and below	Removal (J.L.P.)	Recovered	10½ yr.
18	50 F	Headaches, 3 yr.; slight difficulty in swallowing	Mild left V; left caloric changes	Left tentorium, inferior surface	Removal (J.L.P.)	Recovered (right homonymous hemianopsia)	8 yr.
19	31 F	Headaches, visual loss, unsteadiness, vomiting, and personality change, 5 wk.	Papilledema; nystagmus; bilateral VI; left VIII; left XII; Romberg positive	Left internal auditory meatus	Subtotal removal (J.L.P.)	Stormy postoperative course; blindness, died 3½ yr. later	.....
20	48 F	Occipital headaches, partial deafness, and tinnitus, right ear, 2 yr.; vertigo, unsteadiness, 1 yr.	Papilledema; nystagmus; right V, VII, VIII; right cerebellar signs	Posterior surface petrous bone right, extension anterior to brain stem	Subtotal removal (G.H., J.L.P.)	Died 2 days	.....
21	55 F	Headaches, 3 yr.; staggering, occasional vomiting, 3 mo.	Papilledema; nystagmus; ataxia; right dysmetria; generalized hyperreflexia	Lateral sinus right	Removal (G.H., J.L.P.)	Recovered	?
22	34 F	Deafness and tinnitus left, 5 mo.; staggering, 2 mo.; frequent diplopia	Nystagmus; left VII, VIII; mild left V, left cerebellar	Left internal auditory meatus	Removal (G.H., J.L.P.)	Recovered	5 yr.
23	60 M	Suboccipital pain, 14 mo.; recent loss of hearing right ear, episodes of tinnitus, vertigo, and generalized headaches	Nystagmus; decreased hearing right ear; normal caloric findings	Tentorium, extension into right cerebellopontine angle	1. Suboccipital decompression (G.H.) 2. Removal (J.L.P., G.H.) 6 mo. later	Recovered	5 yr.
24	40 F	Deafness and tinnitus right ear, 3 yr.; headaches and vomiting, 1 yr.	Right V, VIII; nystagmus; ataxia of gait	Jugular foramen, right	Removal (J.L.P.)	Recovered	4 yr.
25	72 M	Progressive mental confusion, 2 yr.	Papilledema; mental confusion; left hemiparesis; bilateral Babinski	Petrosal sinus, left	Subtotal removal (J.L.P.)	Died 6 days (postoperative)	.....
26	50 F	Occipital headaches, vomiting, 1 yr.; difficulty in walking, 4 mo.	Papilledema; decreased hearing left ear; left XII; ataxia, more so on left side	Sigmoid sinus, left cerebellar fossa	Removal (J.L.P)	Recovered	3 yr.
27	44 F	Occipitofrontal headaches, nausea, vomiting, 1 yr.; tinnitus, decreased hearing right ear, 3 wk.	Nystagmus; right V, VII, partial VIII	Apex of right petrous pyramid (posterior surface petrous bone)	Removal (G.H., J.L.P.)	Recovered	3 yr.
28	54 F	Right tinnitus, partial deafness, 5 yr.; right complete deafness, 1 yr.; unsteady gait, 1 yr.	Nystagmus; right V; right VIII; ataxia right; Romberg positive	Right internal auditory meatus	Removal (G.H., J.L.P.)	Recovered	2 yr.
29	50 F	Occasional vertigo, 8 yr.; episodes of diplopia, progressive left hearing loss, and left tinnitus, 4 yr.; left-sided weakness, 6 mo.	Nystagmus; partial left V; left VIII; left-sided ataxia; ataxia of gait	Left internal auditory meatus	1. Subtotal removal (G.H.) 2. Further subtotal removal 1 mo. later (G.H., J.L.P.)	Recovered	2 yr.

* Numerals indicate any cranial nerve involvement, whether partial or complete.

deaths, a number of the procedures were palliative, since the tumor could not always be completely removed, even with multiple operations. Of his seven patients with acoustic syndrome, the tumor was considered inoperable or could be only partially removed in six patients, and these died from four months to three years after operation. Two patients with tumors in the basilar groove and extending into the middle fossa died within seven months of operation. Of the 15 patients with subtentorial and recess tumors, 9 survived for periods varying from 8 to 24 years, with no sign of recurrence. These tumors were for the most part global, arising from the lateral sinus and tentorium.

Castellano and Ruggiero,[2] in analyzing the 71 cases of Olivecrona's series (10 with operation by Norlén), have given a critical evaluation of the mortality in relation to the anatomical origin of the tumors. In the 70 patients operated on, there were 22 operative deaths. There were 30 cases of meningioma of the posterior surface of the petrous bone, the largest number of the group, in which there were 12 operative deaths. Four of 8 patients with clivus tumors died as a result of surgery, while there were only 4 direct operative deaths among 21 patients with meningiomas of the tentorium.

The longest survival in our series is 16 years (Case 4), and 16 of the 29 patients are known to be living at the end of the 20-year period. Thirteen patients have had a useful survival for more than 5 years, and 9 for more than 10 years. (One of these, Case 1, made a good recovery and survived 14 years after operation, then died of bronchopneumonia.) In almost every instance the patients either returned to their former occupations or were capable of household duties. Some have had residual cranial nerve palsies but have, for the most part, overcome the cerebellar symptoms. It is interesting to note that two patients (Cases 11 and 15), in whom complete removal could not be accomplished, have had useful survivals of 14½ and 12 years, respectively.

The remaining patients of those known to be living at the present time were operated upon in the last five years, with the length of survival in each case indicated in Table 5. One patient (Case 21), with whom contact was lost, recovered after complete removal (in 1948) of a large tumor attached at the right lateral sinus. Her condition was excellent at the time of discharge from the hospital.

COMMENT

Although the rapid advances in antibiotic therapy in the past 10 years may lower the operative mortality in these tumors in the future, the greatest factor in increasing the survival is early diagnosis. Except in those patients who had cerebellopontine-angle tumors, the presence of a posterior fossa tumor was often long unsuspected. Headaches and unsteadiness, which are the two leading subjective symptoms, are such common complaints among patients in general, and are so vaguely described, that attention is frequently diverted to other conditions. More widespread use of neurosurgical diagnostic facilities will lead to earlier recognition. While we have not as yet demonstrated these tumors satisfactorily by vertebral arteriography, it is possible that this procedure will be utilized oftener in the future and may be of considerable diagnostic value, particularly in those cases without papilledema and with normal skull roentgenograms.

Cranial nerve symptoms, particularly those related to the trigeminal, facial, acoustic, and vagus nerves, should arouse suspicion of meningioma of the posterior fossa, since these nerves are the ones most commonly affected.

SUMMARY

The paucity of information in the literature dealing with meningiomas of the posterior fossa is noted. Twenty-nine cases of meningiomas arising within the posterior fossa and treated surgically during the 20-year period (Jan. 1, 1934, to Jan. 1, 1954) are reported. The cerebellopontine angle was

the most frequent location. Headaches, unsteadiness, tinnitus, and loss of hearing were the most frequent subjective symptoms, while impaired hearing, hypalgesia or hypesthesia of the face, absent or decreased corneal reflex, and facial weakness were the commonest cranial nerve signs. Supratentorial extension of some degree occurred in 24% of the cases. Complete removal of the tumor and capsule was accomplished in 76% of the cases. Two patients have survived for 14½ and 12 years, respectively, after incomplete removal. In some instances the latter may be a more desirable procedure, particularly to avoid serious cranial nerve or brain stem damage. The immediate postoperative mortality was 31.2% for the first 10-year period and 15.4% for the second 10-year period. The need for early diagnosis is emphasized.

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News and Comment

GENERAL NEWS

AAAS Symposium.—A two-day symposium will be held as part of the program of the American Association for the Advancement of Science on Dec. 27 and 28, at Atlanta. The symposium, entitled "Physiological Bases in Psychiatry," will have four sessions: New Psychopharmacologic Agents, Mechanisms of Actions in New Agents, Effects of Alcohol on Brain Respiration and Metabolism, and Alcohol Addiction—Mechanism and Treatment.

Those wishing to take part in this program should contact either Harold E. Himwich, M.D., Galesburg State Research Hospital, Galesburg, Ill., who is a representative of the American Psychiatric Association, or Fred A. Hitchcock, Ph.D., Ohio State University, Columbus 10, Ohio, who is a representative of the American Physiological Society.

Congress of Neurological Surgeons.—The next meeting of the Congress of Neurological Surgeons will be held at the Statler Hotel in Los Angeles, Oct. 27-29, 1955. The secretary of the organization is Dr. Philip D. Gordy, 1007 Delaware Ave., Wilmington, Del.

SOCIETY NEWS

American Neurological Association.—At the 80th Annual Meeting of the American Neurological Association, held in Chicago from June 13-15, 1955, the following officers were elected:

President	Dr. J. M. Nielsen
President-elect	Dr. H. Houston Merritt
First vice-president	Dr. James W. Kernohan
Second vice-president	Dr. Robert B. Aird
Secretary-treasurer	Dr. Charles Rupp
Assistant secretary	Dr. William F. Caveness

Morrell and Ross's "Central Inhibition in Cortical Conditioned Reflexes"

BERNARD WEISS, Ph.D., Randolph Field, Texas

A recent study published in the ARCHIVES [1] attempted to test a speculation of Pavlov's [2] concerning the changes in cortical activity that accompany the conditioning process. Pavlov hypothesized that the association between the conditioned stimulus (CS) and the unconditioned stimulus (US) is mediated in the cerebral cortex by a path of excitation between the CS locus and the US locus. During the extinction period, i. e., when the CS is presented alone, the disappearance of the conditioned response (CR) is ascribed to the spread of inhibitory processes in the cortex.

Morrell and Ross reasoned that one means of putting the inhibition hypothesis to experimental test was offered by the apparent susceptibility of the electroencephalogram (EEG) to conditioning. If a photic stimulus, which tends to inhibit the alpha component of the EEG, is repeatedly paired with a neutral stimulus, such as a low-intensity tone, the neutral stimulus will tend to acquire the alpha-inhibiting properties of the light [3]; the process seems to behave somewhat like an orthodox conditioned response, although it is far more unstable. During extinction, therefore, presuming that such a response has been conditioned in the usual sense, an inhibitory process should dominate the cortex.

The investigators then proposed that the latency or reaction time (RT) of a motor response (key pressing) to the photic stimulus which produces alpha inhibition could be taken as a measure of transmission time from the visual area to the motor area, and thus as an index of cortical inhibition during extinction. They assumed that conduction times from the retina to the visual area and from the motor area to the periphery were constant.

In the study being discussed, the sound-light pairing was used to produce the "conditioned" alpha blocking. Further, the subject was required to press a key as soon as possible after the appearance of the light. The latency of this response (RT) constituted the data of this experiment. (The authors indicated that the advantage of using the EEG, with alpha inhibition as the UR, derived from the possibility of determining the latency of response of the visual area to the excitation produced by the light stimulus. However, these data are not given.)

On the basis of their results, the authors contended that Pavlov's speculations were confirmed. The purpose of the present note is to offer an alternative interpretation of the data which I believe has at least equal validity.

From Morrell and Ross's Table 1, the conditioning procedure seems to have followed the following schedule:

Trials 1 to 15: Sound and light
Trials 16 to 19: Sound (alone)
Trial 20: Sound and light
Trials 21 to 23: Sound (alone)
Trial 24: Sound and light

On Trials 14 and 15, the RT (reaction time) was 0.3 second. (Presumably, this is

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the mean RT of six subjects.) On Trial 20, the RT was 0.6 second, and on Trial 24 the RT was 0.8 second. The authors claim that these results, namely, the increased RT after nonreinforcement, support the Pavlovian hypothesis of inhibitory spread during extinction.

Another piece of evidence that Morrell and Ross cite in support of their claim is based on the effect on RT of changing the foreperiod, or the time interval between the sound and the light. The procedure here was to present a series of trials in which this interval measured six seconds. On two occasions in 21 trials (so far as one can determine from their Table 3), the CS-US interval, without warning to the subject, was shortened to 0.5 second. This produced a lengthened RT, which was attributed to the fact that the response took place during what was normally an "inhibitory" interval. That is, it was assumed that when the response has to be delayed six seconds, an inhibitory process must be active to effect this delay.

I believe that a more parsimonious explanation can be offered. It is based on certain properties of RT which have been reported in an abundant literature.* Specifically, it is founded on the concept of preparatory "set," or "readiness to respond."

Consider the schedule inferred from Table 1. For 15 consecutive trials, the sound and light have been paired. (The CS-US interval is not given.) Then, on the next four trials no reinforcement (light) is presented. On Trial 20 reinforcement is again presented. I contend that the prolonged RT is simply due to the fact that the subject was not prepared to respond. That is, the presentation of the light on Trial 20 was not expected by the subject; so, on the basis of relevant scientific evidence,† the cogency of which is further strengthened by an a priori analysis of the situation, the lengthened RT would be predicted.

A similar explanation can be applied to the other evidence adduced, namely, the increase in RT with an 0.5-second foreperiod when previous trials used a 6-second foreperiod. Moreover, the length of the foreperiod per se influences RT, and most investigators report ‡ a substantial increase in RT when the length of the foreperiod is reduced to less than one second.

It might be objected that the alternative interpretation is really no alternative at all, but merely explanation at another level—that it is not more than a translation of cortical dynamics into behavioral phenomena. The reply to such an objection is twofold. First, since the phenomena on which the conclusions of the original study are based are behavioral, the burden of proof is on translation in the opposing direction, especially when interpretation at a different level needs to invoke assumptions of unknown validity, such as those concerned with the cortical mechanisms of conditioning. Second, the Pavlovian view of inhibition as an independent process bears, in particular, such a heavy weight of negative evidence § that it does not seem to me legitimate to assign to it an explanatory function, even on its own level.

Questions concerning the adequacy of various assumptions and procedures can also be raised, but they seem relatively minor in comparison with those discussed above. It should be noted, however, that alpha conditioning, because of its instability, was probably not the optimal choice with which to test the hypothesis under investigation.

In conclusion, I believe that the results of the Morrell and Ross study can be interpreted in such a way that they do not rep-

* References 4 and 5.

† Preparatory set has been intensively investigated, and Woodworth and Schlosberg, and Teichner, among others, include integrated reviews of the relevant studies. In general, these studies show that an irregularly varying foreperiod (warning period) produces lengthened RT's.

‡ References 4 and 5.

§ See Wendt,[6] for example. In this article, Wendt shows that many phenomena that might be labeled as occurrences of "inhibition" are more reasonably evaluated as instances of one behavior system shifting to dominance over another. Morgan and Stellar [7] provide a more recent and extensive survey of objections to the Pavlovian view.

resent a confirmation of the Pavlovian view of cortical dynamics in conditioning. I further believe that the alternative explanation offered is a more parsimonious one, and that if one is to accept William of Ockham's dictum that principles are not to be multiplied beyond necessity, it is the one that deserves adoption.

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News and Comment

SOCIETY NEWS

American Psychosomatic Society.—The American Psychosomatic Society will hold its 13th annual meeting at the Sheraton Plaza Hotel, in Boston, on Saturday and Sunday, March 24 and 25, 1956.

The Program Committee would like to receive titles and abstracts of papers for consideration for the program no later than Dec. 1, 1955. The time allotted for the presentation of each paper will be 20 minutes.

Abstracts should be submitted, in sextuplicate, for the Program Committee's consideration, to the Chairman, at 551 Madison Ave., New York 22.

Stanley Cobb, M.D.
Chairman, Program Committee

Carl Binger, M.D.
Daniel H. Funkenstein, M.D.
Theodore Lidz, M.D.
I. Arthur Mirsky, M.D.
Harold G. Wolff, M.D.

PERSONAL NEWS

Dr. Sandor Rado Retires.—Dr. Sandor Rado has retired from his position as Director of the Columbia Psychoanalytic Clinic for Training and Research. In his honor a Lectureship has been established in the Department of Psychiatry, Columbia University College of Physicians and Surgeons. Dr. Abram Kardiner has succeeded Dr. Rado as Director of the Clinic, commencing July 1, 1955.

The Nature of Pain

THOMAS S. SZASZ, M.D., Chicago

WHAT IS PAIN?

It might seem pedantic to ask such a simple question as "What is pain?" Indeed, in the expression "physical pain" there is a ready-made answer should such a question arise. We are told that pain is due to something physical, by which it is meant that there is an injury or a dysfunction of the body.

Even at the risk of seeming pedantic, it might be worth while to examine the notion of "physical pain." For not only does this expression plunge us directly into the age-old dichotomy of physical and mental, but it also asserts a causal connection between so-called physical (bodily) events and pain without first clarifying what is meant by pain. This maneuver is at once an evasion of the problem and a sign of scientific impatience. Instead of trying to understand puzzling, sometimes disturbing, phenomena in terms of processes or situations in which they typically arise, we immediately focus our interest elsewhere and speak of causation. Attention is thus shifted from phenomenon A, which is to be "explained," to phenomenon B, which is said to cause it. When we speak of physical pain, for example, the nature of pain is no longer the issue, but, rather, the nature of the bodily lesion "behind" it.

Such "causal explanations" have existed in most areas of human inquiry and have had to be put aside before further understanding could be achieved about a particular problem. I shall mention only one illustrative example of this important philosophical issue. Clearly, a limitless number of instances could be cited from past and present efforts at scientific understanding. Consider the problem of phenomena such as phobias, obsessions, and delusions. Prepsychoanalytic psychiatry did not approach these symptoms by asking what they were or meant, but referred to them in terms of causal notions; i. e., they were due to "heredity" or some disease of the brain. In the early stages of the exploration of a problem it is often easier to find a relevant causal connection between the phenomenon under consideration and some other event than it is to gain insight into the mechanisms or processes operating in the total field within which the phenomenon occurs.

THE BASIC MODEL OF PAIN

The biological function (and meaning) of pain is that of a signal by which the perceptive part of the organism (ego) registers the fact that something is "wrong" (damaging, dangerous) with its structural or functional integrity. This is essentially what we all mean when we speak of physical or organic pain. Moreover, this meaning of pain is not learned from others, but is acquired spontaneously in the process of early childhood development. It is also independent of cultural overtones. Indeed, in this sense of the word, we also consider animals to experience pain.

The foregoing considerations contribute to the view that this type of pain is "objective";

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The opinions or assertions contained herewith are the private ones of the writer, and are not to be construed as official or reflecting the view of the Navy Department or the Naval Service at large. (Art. 1252, Navy Regulations, Oct., 1953).

that is, the experiencing system has nothing to do with it. It simply registers "pain" whenever a "painful stimulus" is present. This view of pain is modeled after a simple stimulus-response concept, the physical basis of which may be thought of as a bell, which rings whenever an electric current is sent through the wires to which it is connected. Thus, in neurology, we speak of pain receptors, pain fibers, and central representations of pain. It is obvious that this is legitimate and useful. Moreover, it is only because we assume that the receptor mechanism in this frame of reference is an invariant factor under normal conditions that we can make inferences about a disorder in the receptor mechanism itself in certain clinical syndromes (e. g., syringomyelia). The view that the receptor mechanism does not contribute qualities of its own to the final experience is a fundamental feature of the whole concept of "sensation." Thus far we have considered what is often referred to as physical pain sensation. This abstraction implies that under the given circumstances any similar organism (if intact) would experience pain.*

In addition to this basic meaning of pain as a perception that "something is wrong with the body," we could describe another facet of the experience as a message. The message is sent, so to speak, from the body to the ego, and it commands the latter to take steps to protect the organism from the danger at hand.† The message could be verbalized in this way: "There is danger here—Stop!"; and, further, "Remove the part," or "Put the part at rest." If we injure a part of our body, this is what we do automatically.

This, however, is not all there is to pain as we know it in human beings living in complex societies. Nevertheless, we often talk and act as if all pain experience had to be forced into this scheme and must be understood in these terms. Such attempts do violence to clinical facts and lead to misunderstanding between patient and physician. In what follows I shall describe briefly some other phenomena which are also designated by the term "pain." In this way we will distinguish several levels of "pain concepts." The evolution of higher levels of meaning parallels a general increase in the complexity of our cerebral and mental organization. One of the manifestations of this tendency toward more complex symbolizations is the growth of the meaning of "pain."[3] I shall also attempt to show how the more complex meanings of pain evolve from and lean upon the primary model of pain.

DEGREES OF SYMBOLIZATION IN THE CONCEPT OF PAIN ‡

The primary model of pain is a construction based on a phenomenon within a single organism. Insofar as we speak of communication (of a message), it is from the body to the ego. In other words, we deal here with a one-body frame of reference. Accordingly, there is no question of validation, and no question of what is meant by the term "body." Body denotes here whatever is so recognized by the ego. This may be something very vague in infancy and something more structuralized in adulthood. In any case, there can be no question as far as the ego is concerned about whether a pain felt in the abdomen is "really" there or not. As I tried to demonstrate elsewhere, to the experiencing ego all pain relates to the body.[5]

We may distinguish a second category of pain when we bring another person into the field. It so happens that in the process

* Drever[1] gives the following definition of sensations: "The ultimate and irreducible aspect or element of sense perception, dependent upon the stimulus affecting a sense receptor; really an abstraction, but generally discussed, especially in physiology and psychophysics, as if it were an elementary experience; the process of sensing."

† This occurs reflexly, or perhaps often unconsciously, and what is here spelled out must not be taken literally. The value of these constructions will become apparent when we relate other, more complex and often more obscure, meanings of pain to these primary models.

‡ The concept of different levels of symbolization constituting different levels of language was developed by workers in symbolic logic (cf. Reichenbach, References 2 and 3).

of childhood development the expression of pain leads other persons to minister to the child in ways designed to relieve the painful state. It follows that while the expression of feeling pain is at first very likely spontaneous, and not in itself goal-directed, the sequence of events which ensues establishes this as a fundamental method of asking for help.§

Insofar as the term "pain" refers at one and the same time to the ego's perception of a bodily disorder and to a request for help, it is used to symbolize a more complex phenomenon than that subsumed under "primary model pain." This is the basis for regarding "pain" as being used at two different levels of symbolization in the foregoing two situations.

The introduction of a second person (or of several others) into the situation in which we speak of pain accounts for most of the ambiguities which we encounter in clinical work and terminology. For when a person reports a painful experience to another, he speaks in terms of his notion of his body (that is, his own body image), and the listener receives and interprets the message in terms of his own notions. All of this is self-evident and has been pointed out by others as being responsible for many of our problems couched in the terminology of mind versus body.[4]

The meaning of pain in this second sense contains all of the meanings belonging to the primary model of pain. In addition, it has acquired the added meaning of asking for help from another person. The purpose of the request is to obtain relief from the painful experience and to secure help in dealing with the danger signaled by the pain. In order to secure this help, it is essential that the meaning of the dangerous state be conveyed to another person. Whether this is easy or difficult depends upon how well the persons who are interacting understand each other. The distinction between physical and mental pain presupposes a two-body frame of reference. Physical pain denotes agreement, and mental pain denotes disagreement between sufferer and observer. The agreement (or disagreement) may relate either to pain as it expresses a state of affairs or to pain as it expresses a wish or command. In the first instance it is as if the observer —let us now call him physician—were to say to the patient, "Yes, I understand that such and such a process is going on in your body and this causes your suffering." In the second instance, agreement between patient and physician need not refer to the source of the trouble, but may simply mean, "Yes, I will try to help you." The implications of disagreement between the two participants are the reverse of the former assertions.

In the third concept of pain, one person addressing himself to another with the complaint of pain becomes the focus of our attention. Previously we noted that the phenomenon of pain may be divided into two components: one, a signal informing the ego of a danger in relation to the body, and the other, a message requesting help from another person. The former meaning of pain refers to anatomical and physiological matters and will be designated accordingly as the medical meaning of pain. The latter refers to human relations and may be called the communicative meaning of pain. To add that these two components of pain never exist separately, or in "pure culture," would be stating a truism. Let us proceed therefore with further consideration of the third category of "pain," in which the predominance of the communicative meaning of pain is the characteristic feature. The practical importance of this concept of pain is the greatest at the present time. The medical meaning of pain has been the subject of clinical investigations, as well as of the basic medical sciences throughout modern medicine. Moreover, there is adequate terminological clarification in this area, so that there is a minimum of confusion as to what is meant

§ If the expression of pain is so fundamentally associated with asking for and getting help, it follows that pain suffered in silence, or persistently unrelieved, may readily be interpreted as punishment. It seems to me that these issues contain the biological and interpersonal roots of our everyday ideas concerning reward and punishment, and its corollaries "worthy" and "sinful."

when medical men, other scientists, and patients speak of phenomena belonging into this category.

The opposite state of affairs characterizes the status of pain as a communication concept. It has not been studied to any great extent either by the medical or by the social sciences. There is also much misunderstanding between people when reference is made to pain of this type. In fact, there is a common tendency to try to reduce all pain to being nothing more than a signal or referent concerning some bodily disorder (even this is only one part of the primary model of pain). This, then, is "real" pain. All other pain is somehow more or less "imaginary."‖

In actual fact, observation tells us that in many instances of pain, the term may contain only a nucleus of a meaning according to the primary model of reference to bodily disorder. Instead, pain may be chiefly a command addressed to a particular person, from whom assistance may be expected, to come and to help. Or pain may be addressed to someone not because we need and expect his help, but because we feel he owes us something. This, then, may be a way of enforcing payment of our "just dues." There are a number of possible meanings within this category; some of these will be illustrated by clinical observations.¶

We may summarize the chief motives of the communicative meaning of pain as follows: It arises out of a need which may be that of a bodily disorder, or it may be another need. The experience and expression of pain is an attempt to satisfy this need. While the nature of the experience and its expression lean upon the primary model of pain, the actual meaning of the experience differs essentially from that of the primary model.

OBSERVATIONS AND INFERENCES

Clinical observations concerning cases of so-called psychogenic pain are readily available. Situations in which a patient feels and complains of pain and in which the physician can find no organic disease or dysfunction to "account" for it are familiar to psychiatrist, internist, sociologist, and layman (patient) alike. What is common and familiar, however, is not necessarily correctly understood. Indeed, the very frequency of a problem may make one impatient in the face of uncertainty, and thus favor the acceptance of pseudoexplanations. The notions of "physical" and "psychogenic" pain are in the nature of such pseudoexplanations.

First, let us consider a hypothetical case: A child of school age complains of "pain" # to his mother in the morning. We say that the child complains of pain because he does not want to go to school. This interpretation is further strengthened by the assertion that the child is afraid of something in the school situation, or he is fearful about leaving mother and home, and so forth. The implicit inference in this construction is that the child does not really have pain. He only says so

‖ One wonders if the terminology (and philosophy) of mathematics has not had an influence on medical matters relative to this issue of "real" and "imaginary" pains. In mathematics, of course, we speak of real and imaginary numbers. Today this no longer means to the mathematician that so-called imaginary numbers are any more or less "real" than so-called real numbers. However, when imaginary numbers were first discovered, the situation was probably different, in that real numbers were felt to bear some transcendental relationship to "physical reality"; in contrast to this, imaginary numbers must have seemed as man-made, and thus not quite "real." The error of such distinction, immemorialized in this example in the terms "real" *vs.* "imaginary," is now a part of the history of scientific philosophy.[2]

¶ If we look upon pain as a communication, it follows that the question of whom the patient is addressing with his message is of crucial importance for a correct understanding of the phenomenon. We touch here on a very intricate problem, and I want to do no more in this connection than to indicate its presence. Thus, we must consider the possibilities that the pain is addressed principally to someone in the patient's current life situation or that it relates to a childhood image, or it might be addressed to a group or organization, or it might not be addressed to anyone in particular but be a kind of desperate cry for help to anyone who will listen, and so forth.

This might be abdominal pain or headache, or pain referred to any other part of the body.

because he has learned that this claim will bring about the desired result.

The chief differences between this interpretation and the one suggested in this paper are the following: 1. I maintain that it is meaningless to assert that the child "really" does not have pain, but only says he has it. Our very task is to find out why he expresses himself in this way. 2. The interpretation given above as to why the child "claims" to have pain is taken as the meaning of the word "pain" in this situation. This example may be regarded as an illustration of the communicative meaning of pain, in sharp contrast to its medical meaning. In all situations where the direct communication of a need is inhibited, either by external reality, or by inner standards, or by a combination of the two, pain may be experienced and expressed. In this respect pain is a neurotic symptom, brought about by a regressive compromise solution of a currently insoluble conflict.

It is important to note that all patients with the predominant symptoms of pain whom I have observed as a psychiatrist were referred to me by physicians. None came of his own "free will." This is consistent with the thesis that to the person experiencing pain the symptoms connote some derangement of the bodily machinery, and accordingly medical or surgical relief is sought. Psychiatric referral implies to the patient that his complaint is essentially not believed by the physician. I have found discussion of this issue at the very outset helpful in overcoming at least this additional burden which faces both patient and psychiatrist in their quest for a better comprehension of the meaning of pain.

A girl in her late teens came for psychiatric treatment after an incapacitating illness of about two years' duration. Her chief symptoms were attacks of severe pain, referred to the abdomen, pelvis, and lower back. There were also episodes of anorexia and occasional vomiting. At first she did not accept the possible rationality of psychiatric treatment. She came only because over a period of two years repeated medical examinations resulted in conflicting diagnoses and because the many treatments tried were of no avail. Finally, she went to a large diagnostic center, where the need for psychiatric treatment was impressed upon her, as well as upon her family physician.

The patient lived in a distant community, making it impossible for her to make frequent visits to the office. She had an average of two appointments a week for a period of a year and a half. During the first six months, many appointments were broken because of attacks of pain for which she remained at home, confined to bed.

As is true of all excerpts from psychiatric observations, it is not possible in a few paragraphs to do justice to all of the clinical material as it emerged in the process of psychotherapy. It must be borne in mind, therefore, that I shall cite only a few highlights of the history and those specific factors from the therapeutic interaction which are relevant to our present focus on the problem of pain.

The patient was reared in a well-to-do Catholic family in a small town. She had three older sisters and one younger brother. Approximately three years before the beginning of treatment, the mother underwent an operation. There was some concern about the possibility of a malignant tumor, but at surgery it was established that the symptoms were due only to extensive fibroids. The family was relieved. Then, suddenly, the mother died of a massive postoperative hemorrhage. The patient was stunned, as was the whole family. Indeed, no one in this family seemed fully to recover from this loss. The father became depressed and withdrawn. The older sisters tried to help, but they, too, had been dependent on the mother, even after they were married and had families of their own. In this situation the patient found it impossible to "let go" and mourn the loss of her mother. Not only could she find no support for her own needs in this moment of stress, but, realizing her father's suffering and the older sisters' ineffectiveness, she began to feel increasingly that she should take an active role in managing the household and in comforting her father. Her father, however, remained depressed, and about a year later he drove his car into the abutment of a bridge and died immediately. Everyone in the family regarded this accident as a suicide. Shortly after the father's death, the patient became ill with the symptoms described earlier.

When the patient first came for psychiatric treatment, she appeared to be an intelligent and introspective girl, who suffered much but bore it stoically. She was neither depressed nor anxious, but, on the contrary, appeared well composed. She also "looked ill" in that vague and undefinable manner in which people give the impression of being, as we say, "organically sick." Indeed, had it not been for the repeated physical examinations and the recent tragic events, I would have been strongly tempted to feel with the patient that hers was not a "psychiatric problem."

On the basis of the historical material, much of which the patient related during the first few hours, one could surmise that because of the magnitude of the traumata to which this patient was exposed, she had been unable to integrate them and that this failure to resolve the losses which she experienced may then be related to her present illness. It also became apparent that the patient, in her life situation, was quite isolated from people. While she lived in the home of an older sister, with the sister's family and with her younger brother, she was quite estranged from them. They did not understand her, and the lack of understanding grew monumentally as her undiagnosed illness dragged on and baffled, worried, and angered the family. She was also alienated from her friends and her teachers at school.

About two months after the beginning of psychotherapy the patient canceled several appointments because of severe pain. While she had experienced various symptoms during the preceding two months also, they did not seem to have the same implication they had now, namely, that she was stopping the treatment. To some extent, this was anticipated, and it had been discussed with her. And at this time she was urged in a rather authoritative manner to continue the treatment. The fuller significance of these events did not become clear until later.

The loss of her parents and the repeated "disappointments" in relation to her sisters and physicians led her to feel quite alone. She felt that no one really cared whether she was well or ill, and, further, that no one understood what was wrong with her and that no one was capable of helping her. These notions, which have well-known ubiquitous childhood sources in all of us, were reenforced by her recent life experiences. The intense attacks of pain (for which her family physician, responding to the calls of her panicked family, gave repeated injections of morphine) in this last episode had, at least among other meanings, the function of protecting her from the dangers of a developing positive transference. My urging the patient to continue the treatment gave her the realistic support and reassurance to which one is entitled when one's trust in human helpfulness is shaken.

As she became more certain of the reliability of the therapeutic situation, she was able to review and to come to grips with the circumstances of her parents' deaths and the reactions of the various members of the family to these events. Her distrust of physicians and the misunderstanding which ensued from her painful illness, for which no clear physical cause could be found, became conscious and understandable and thus comforting, rather than confusing, to her.

The patient was greatly improved after about one year of treatment. Pain occurred very infrequently. Instead, she was able to experience a much broader spectrum of human emotions and could regard these as reflections of her relationship with the people about her. She was no longer alienated from her family. She concluded that they had little in common, and she now had a consciously more distant and more comfortable relationship with them. She also entered on a training program for professional work, from which she obtained much satisfaction.

This case illustrates several communicative meanings of pain. Not only was the pain of this girl at first a request for help addressed to her older sisters and later to physicians, and subsequently an aggressive, frustrated complaint of "You see, you still have not done anything for me . . . "; but it had still another function, which seemed to me quite important. This was its function as a warning signal of an impending danger. It was as if the patient, having lost both parents, had no really significant object left to lose other than her body. Then, as if to make sure that she would not be taken by surprise again, as she was by the death of the mother, she experienced the warning signal in a chronic manner. In this way, the warning itself became—as it always does in such instances—a source of security. This accounts, in part, for the patient's composure during her illness. I may add that the foregoing interpretation of the function of pain is analogous to our ideas concerning anxiety and "distrust" as defenses against the transference, in the psychoanalytic situation. By this, we understand the patient's anxious expectation of being deserted or let down in some manner by the analyst. This fear either echoes some actual childhood (or later) event or expresses the dread of aloneness based on some other source. In other words, if we look upon the body as an object of the ego,[5] it may be possible for us to expand the concept of transference from human objects to the body. I think that this phenomenon does occur. In this case the body functioned as a transference object, substituting for both the mother and the father. The experience of pain is the appropriate signal warning of danger in relation to the body. In this case, it warned—in the last analysis—against the

danger of losing the parents, thus recreating the unsolved traumatic situation in the hope of eventually solving it. The similarities between the structure of this symptom and the structure of melancholia is evident. I have discussed the relationship of pain to depression and paranoia in greater detail elsewhere.[6]

A man in his late 30's was referred for psychiatric consultation by the medical service because of persistent abdominal pain. He was a chief hospital corpsman, who had completed more than 20 years of service, with an excellent record. About 10 years before the present illness he had had a duodenal ulcer. This had healed within a few months and had not recurred.

The symptom of abdominal pain, poorly localized over the middle and left upper parts of the abdomen, had started about three years before. Medical and roentgenological examinations did not reveal any significant abnormalities, either at the time of the onset of symptoms or at the time of my contact with him. As a result of the pain, however, the patient soon received a somewhat easier and more comfortable work assignment. This practical gain had no apparent effect on the progress on the patient's orientation to his abdomen. The complaint remained about the same. Clearly coincident in time with the completion of his required tour of duty which made him eligible for retirement, the intensity of the pain and of the disability increased. As a result, he was placed on limited duty. When repeated and exhaustive medical studies revealed no positive findings, a psychiatric evaluation was requested.

The functional value of the symptom for the patient was readily apparent. Indeed, it seemed as if all significant issues in his life were translated, so to speak, into the language of pain, and were then expressed in such a manner that neither the patient nor those to whom he addressed himself really knew what he was saying. Issues of less importance escaped this fate and could be discussed without such symbolic transformations.

The following examples will illustrate what I mean by the translation of important issues into the language of pain. Obviously, the patient was facing an important change in his total life pattern. His entire adult life had been devoted to Navy service. Having enlisted in his late teens, he was still a young man and was now faced with the task of making a transition to civilian life. He himself, however, did not think this was a problem. He had located a job involving work similar to that which he had done in the Navy. He did not feel that there was any "problem" there. Similarly, in his personal relationships he could not detect or express any conflicts. The expression of pain was not so inhibited. Without attempting to document further my inferences with specific observations, I would like to suggest the following interpretation of the pain syndrome described.

Before doing this, however, let us state briefly the questions (phenomena) which we are trying to answer (explain). They are these: 1. Why does the patient feel pain in the absence of demonstrable disease? 2. Why does the pain persist? 3. Why is there no physiological (objective) manifestation (e. g., facial expression of suffering, tension, etc.) present, such as is usually associated with (primary model) pain? 4. What is the meaning, if any, of the mutually frustrated and hostile patient-physician interaction which invariably ensues in situations of this type?

If we look upon the patient's productions as we are accustomed to doing in psychiatry, that is, as communications,* the problem is to find out what the patient is saying. What this man was saying could perhaps be paraphrased as follows: "I need something—some help, support, guidance—now that I am about to leave the Navy and must enter a pattern of life with which I am not familiar. Will you please help me?" As no help is forthcoming, it reenforces the already existing ambivalences to the organization which "rejects" him after so many years of service. This initiates a vicious cycle, since the patient is particularly blocked in his ability to acknowledge and live with hostile feelings toward anyone with whom he has a significant relationship. The persistence of the pain now becomes a "complaint" and retribution. This should be taken literally, to mean that the patient is now complaining against those who he feels have let him down. Yet this is done symbolically, maintaining a conscious attitude of friendliness. The final meaning of pain thus might be thought of as the patient saying, "You see, I have done my duty, but you have not done yours [namely, to help me]." This justifies his anger and feeds into the retributive meaning of pain. Once this process is set in motion, it would follow that each step strengthens the motives for pain. The symptom thus becomes increasingly useful for the patient's psychic economy.

We may summarize the symbolic transformations which the concept "pain" has undergone in this case as follows: 1. The pain experience is an expression of a need for help (thus, also an intrapsychic defense

* This is in contrast to the usual medical orientation to this symptom. Pain is thought of not as a potentially multivalued communication, but only as a communication about the body. In other words, it is as if the physician was saying, "If this statement does not refer to the body, then it is nonsense."

against anxiety). 2. The communication of pain is a request for help. 3. When the request is frustrated, the persistence of the pain becomes a symbol of being rejected: "It still hurts. . . . " 4. The repeated complaint of pain is also a disguised aggression (retribution) against the frustrating, rejecting authority (physician, Navy, parent, etc.). The unyielding symptom becomes upsetting to the physician. It will be seen that the structure of this symptom bears some important similarities to that of the paranoid delusion of persecution. I have discussed some aspects of this problem previously in connection with the nature of phantom pain.[6]

SUMMARY

Pain is customarily divided into two large categories, designated as physical and mental. These terms offer a causal differentiation instead of a clarification of pain as a concept involving various levels of complexity and meaning. The purpose of this paper is an examination of the nature of pain, based on clinical observations and on a consideration of philosophical, semantic, and psychiatric knowledge.

It is suggested that we distinguish "pain" at three levels of symbolization, arranged in a hierarchy of increasing complexity. The first concept of pain is that of a signal by which the perceptive part of the organism (ego) registers the fact that there is something "wrong" (damaging, dangerous) with its structural or functional integrity. This is thought to be the biologically given meaning of pain. This meaning is acquired spontaneously, is independent of cultural overtones, and is the sense in which we can also speak of animals having pain. In this concept of pain there is only one person involved. Insofar as we regard the phenomenon in terms of communication, we consider that a message is sent from the ((injured) body to the ego, commanding the latter to take protective steps to prevent further damage. Since this is a one-body frame of reference, there is no question of validation and no possibility of misunderstanding between persons as to the meaning of messages.

In the second concept of "pain," the word refers to a situation in which there are two or more persons present. All pain experienced by someone other than ourselves falls into this (or the next) category. The expression of pain is shown to be a fundamental method of asking for help. Any attempt to communicate the experience of pain to another person involves problems of validation and possible differences in the meaning of the concept "body," about which pain warns the ego and the observer.

The third concept of "pain" refers to that group of phenomena in which the meaning of pain lies predominantly in its communicative aspect. In situations belonging to this group, while the word "pain" is used (as it is on all three levels), the actual (correct) meaning of the word here depends on the understanding of some major symbolic transformations. In other words, pain in this context may no longer denote a reference to the body. Instead, it may be a request for help, or a complaint about being unfairly treated, or an attack and a retribution against a needed but unconsciously hated object.

Further, since the body may function as an important object of the ego, it can acquire special meanings by virtue of transferences from other objects (persons). Pain may then function as an affect warning the ego of the danger of loss of object.

Clinical observations are cited to illustrate the foregoing theoretical constructions and to show their relevance to the work of psychotherapy.

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Agenesis of the Corpus Callosum

A Report of Two Cases in Siblings

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The purpose of this report is to record two cases of agenesis of the corpus callosum in siblings and to discuss some of the possible causes of its occurrence. The literature on this anomaly was reviewed by Carpenter and Druckemiller in 1953.[1] They found 45 cases in which encephalograms had been obtained, and the diagnosis had been made during life in 43. They added two cases of their own. It is obvious that not all cases have been reported, and that therefore this anomaly occurs far more frequently than these figures would suggest. Their report does not include any instance of two cases occurring in the same family.

CASE MATERIAL

The patients were two sisters, Carol T. and Gail T. (Cases 1 and 2 respectively), admitted to the Montreal Neurological Institute on March 18, 1952, for investigation of mental retardation and physical underdevelopment.

The father, aged 43, was well and had never had any neurological complaints. The mother, aged 36, was well except for a prolapse of the uterus, which developed after the birth of her fourth baby. She did not have any x-ray examinations or treatments during her pregnancies. Her first pregnancy resulted in a spontaneous abortion in the second month. Then she gave birth to Carol, aged 7 at the time of admission. A normal son was born the following year (birth weight 6 lb. 8 oz. [2948 gm.]), and two years after this, Gail was born (aged 4 at the time of admission). After an interval of three years, a normal girl was born (birth weight 6 lb. 12 oz. [3063 gm.]). The normal girl is right-handed, and the normal boy was left-handed in early life but was trained to be right-handed.

The families of the parents were not related. Both parents are right-handed. A first cousin of the father died in a mental hospital at age 29, after becoming psychotic at age 25. The family history was carefully investigated for epilepsy, mental retardation, and other neurological disorders and was found to be negative.

CASE 1.—Carol T., aged 7 years. The mother's pregnancy and the birth were uneventful. The patient weighed 3¾ lb. at birth and was always a feeding problem. She sat up at 1 year and began walking at 2 years 4 months. Bladder and bowel training had been achieved only two months before admission. She had had rheumatic fever at 4 years of age and mumps three months before admission. There was no history of fits. She was left-handed. Physical examination showed that she was small and undernourished (weight, 33 lb.) and very severely retarded in mental development. She would say only "mummy," "daddy," and "hello." She was fretful and restless and cried most of the time she was in hospital. A reduction in the amount of crying could be achieved by placing her in the same bed as her sister. There was no evidence of interest in the surroundings, and no relationship was established with any member of the staff during hospitalization. Feeding was a difficult problem.

Her head circumference was 47.5 cm., which is at the lower limits of normal for the age of 7, and the ear-to-ear diameter was 29 cm. She had a pilonidal sinus. The physical examination was otherwise unremarkable.

The electroencephalogram was considered borderline normal. It was noted that the brain waves showed a higher amplitude over the right hemisphere. The skull x-ray showed some unusual flattening posteriorly. The left side of the vault was slightly thicker than the right, and the floor of the skull on the left was slightly higher than on the right, suggesting a smaller left hemisphere.

The pneumoencephalogram revealed that the right lateral ventricle was slightly enlarged, and the left moderately enlarged, with maximum enlargement of both ventricles posteriorly. The lateral ventricles were widely separated, and an enlarged third ventricle could be seen extending

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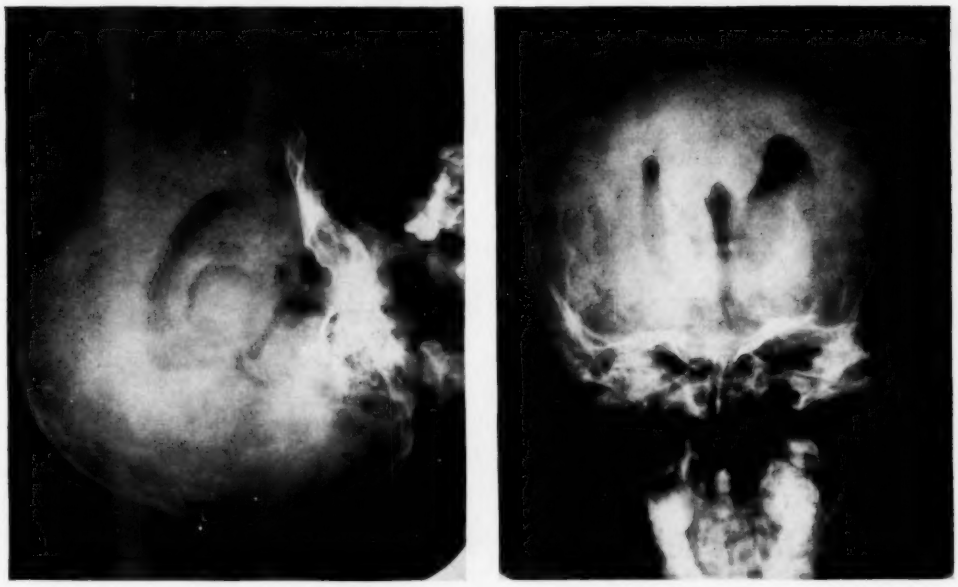
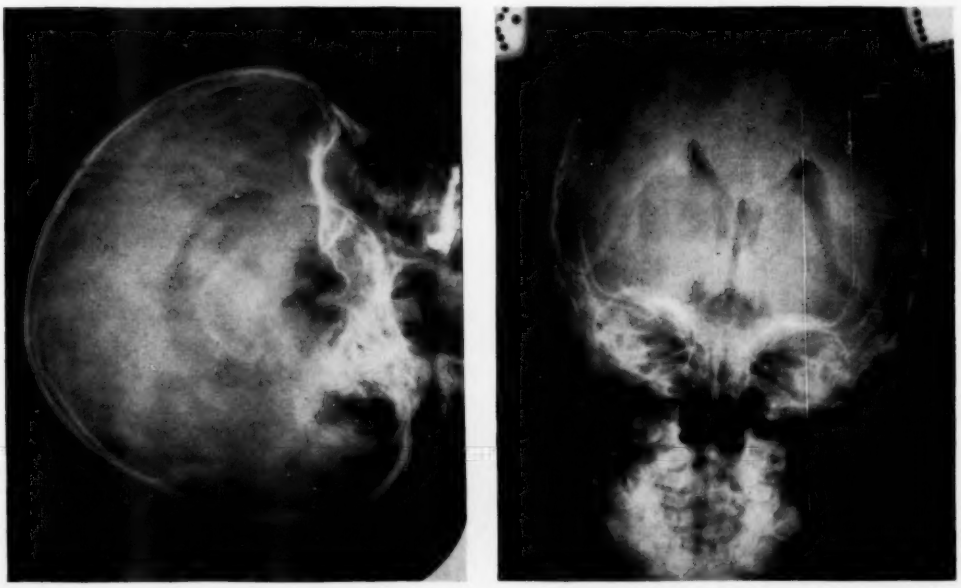


Fig. 1.—Brow-up lateral and anteroposterior projections of encephalograms of Case 1.

superiorly (Fig. 1). Dr. D. L. McRae made a radiological diagnosis of complete agenesis of the corpus callosum.

CASE 2.—Gail T., aged 4 years. The pregnancy and birth were uneventful. She was said to have been born three weeks prematurely and weighed 3 lb. (1360 gm.) at birth. She began to walk about six months prior to admission and had never walked well. She had had mumps at the same time as Carol. There had been two episodes of unconsciousness, one in April, 1951, and one a week before admission to hospital. The spells were accompanied

Fig. 2.—Brow-up lateral and anteroposterior projections of encephalograms of Case 2.



by stiffening of the limbs and rolling of the eyes upward. She was left-handed, like Carol.

On physical examination, it was noted there was a definite resemblance between the sisters, both in facial features and in body build (weight, 21 lb.). Her behavior was essentially the same as that of her sister. The head circumference was 46 cm. and the ear-to-ear diameter 27 cm. She also had a pilonidal sinus. The neurological examination was negative except for a questionable left Babinski sign.

Gail's electroencephalogram was considered normal, as was the x-ray of the skull except for the small size of the skull and some posterior flattening. The pneumoencephalogram revealed the lateral ventricles to be over average in size. They were relatively larger posteriorly than anteriorly. The third ventricle was not widened, but it was unusually high, and its roof was well above the levels of Portions 1 and 2 of the lateral ventricles but not above the level of Portion 3 (Fig. 2). Dr. D. L. McRae also considered this case a typical example of agenesis of the corpus callosum. Blood and CSF Wassermann reactions were negative, and CSF proteins were normal in both cases.

Blood groupings were as follows: Father: O, Rh_0; Mother: A, Rh_0; Carol: A, Rh_0; Gail: A, rh.

COMMENT

The diagnosis of agenesis of the corpus callosum in these two cases was based on the characteristic pneumographic findings.

The presenting symptom in both cases was severe mental and physical retardation, though Gail T. had had convulsive seizures. There were no features in the history or the neurological examination pointing to the particular type of congenital anomaly present. Both children had a pilonidal sinus, a condition which does not appear to have been reported previously as occurring in conjunction with agenesis of the corpus callosum.

The review of this condition by Carpenter and Druckemiller [1] indicates that the commonest presenting feature is mental retardation or seizures or both. However, it must be pointed out that agenesis of the corpus callosum may occur without mental retardation or seizures. There are no physical or neurological findings pathognomonic of this particular anomaly, and the diagnosis is only established by pneumography or postmortem examination.

In view of the occurrence of two cases of agenesis of the corpus callosum in siblings, it will be of interest to consider possible causes of this unusual anomaly. Almost nothing is known of the causes in humans.* Marburg [6] distinguishes "genuine" callosal defect, due to a developmental defect of the commissural plate during the first two weeks of embryonic life, from defects secondary to some destructive process, such as inflammation or porencephaly.

The growth-disturbing agent in the genuine type must a priori be genetic, or an intrauterine environmental factor, or a combination of the two.[2] So far no such agent has been positively identified.

Defects of the corpus callosum, with presence of the longitudinal callosal bundle, have been described as a hereditary condition in mice.[5] Three distinct types of defect were observed: (1) complete absence of the corpus callosum; (2) partial corpus callosum present anteriorly, and (3) partial corpus callosum present posteriorly. The longitudinal bundle (a structure which does not appear in normal mice) was considered to be composed of fibers from the cells of origin of the corpus callosum. A similar structure is said to occur in human cases of absence of the corpus callosum.[6] Another hereditary type of corpus callosum absence occurs in mice suffering from hereditary hydrocephalus, but here the defect is secondary to distention of the ventricles and thinning of the cortex.[3]

On the environmental side, it is interesting to note that agenesis of the corpus callosum occurred in the offspring of rats irradiated (100-400 r) on any day from the 9th to the 19th day of gestation.[4] Irradiation in the early part of this period also caused a number of other gross malformations of the cerebrum. These became progressively less severe as the radiation was given later in gestation; but as term was approached, cerebellar defects began to occur with increasing frequency and severity. An association of absence of the corpus callosum

* References 1 and 7.

and cerebellar defect has been described also in the human brain.[7]

There has been, until now, no evidence of a possible hereditary influence in the causation of agenesis of the corpus callosum in man; it should be pointed out, however, that most of the family histories given in the published case reports are extremely inadequate, if present at all.

The occurrence of the defect in siblings, as reported above, does not, of course, mean that the condition is genetic, though it does suggest the possibility. In this regard, it is interesting to note that corpus callosum agenesis has recently been observed in both members of a pair of identical twins.† If a rare recessive factor is involved, it can be predicted that further cases occurring in siblings will soon be discovered should an effort be made to examine the siblings of known cases. Furthermore, the defect would be expected to occur relatively often in the offspring of consanguineous matings. A statement about the presence or absence of parental consanguinity should therefore be recorded in all cases of this defect.

SUMMARY

Two cases of complete agenesis of the corpus callosum in siblings are reported. The main clinical features in both cases were severe mental retardation and physical underdevelopment. The diagnosis was made by pneumography.

The occurrence in siblings suggests the possibility that this anomaly may be genetic in origin.

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Dr. Francis L. McNaughton gave help and encouragement in the preparation of this article, and Dr. D. L. McRae gave us the use of the radiological material.

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Electro-Ontogenesis of Cerebral Activity

Forms of Neonatal Responses and Their Recurrence in Epileptic Discharges

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As Witteridge [41] noted in 1950, there is still a great discrepancy between the enormous literature on the electrical activity of the cerebral cortex and the little agreement on its interpretation. The difficulties in the interpretation of the normal (and abnormal) electroencephalogram (EEG) may spring in part from our attempt to understand the full complexity of adult activity without knowledge of ontogenetically earlier, simpler stages. Though we have systematic studies of the ontogenesis of the EEG in man (Lindsley *; Smith †; Henry,[19] 1944; Gibbs and Knott,[17] 1949; Grey Walter,[18] 1950; Gibbs and Gibbs,[16] 1953; Kellaway,[24] 1953; Melin,[31] 1953), there has been no systematic experimental study on laboratory animals. Instead, we have scattered reports dealing with some aspects of electro-ontogenesis, largely on the guinea pig and rabbit. The study reported here represents an attempt to describe the general trends of postnatal development of the electrical activity of the cortex in the kitten. It seems advantageous to study this in the cat for the following reasons: (1) Most of the published data on the activity of the adult cortex relate to the cat; (2) the neocortex of the newborn kitten, in contradistinction to that of the guinea pig, is immature and shows little activity at birth; (3) consistent studies of electrocortical phenomena of deep barbiturate anesthesia are difficult in the rabbit because of the narrow margin between excessive activity and death (Forbes and associates,[11] 1949).

Kornmüller [25] (1935) recorded spontaneous activity from the visual cortex of the rabbit on the sixth day after birth. Marinesco, Sager, and Kreindler [30] (1936) showed that the "bioelectrical" activity of the newborn guinea pig is greater than that of the cat. Jasper, Carmichael, and Bridgman [23] (1937) found in the guinea pig "definite though not invariable" effects of stimulation at 60 days' gestation. Pentzik, as cited by Grey Walter,[18] noted in the rabbit that the electrical activity began to resemble the adult pattern about the 14th day. Flexner, Tyler, and Gallant [10] (1950) recorded rhythmic potentials from the cortex of the fetal guinea pig on the 46th day of gestation. They made important observations on the morphological and biochemical changes that accompany the differentiation of neuroblasts into neurons. Bishop [2] (1950) observed in the rabbit that the triphasic strychnine spike is evident at birth but has an extremely long duration. Hunt and Goldring [20] (1951) found in the rabbit a response of the visual cortex to electrical stimulation of the optic nerve at birth, although with long latency and marked fatigability.

For many years several investigators have tried to reproduce in the laboratory repetitive "spike-and-wave" discharges like those seen in the young human epileptic. Gibbs and Gibbs [16] have summarized the attempts to

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A preliminary report of this study was published in the May, 1954, issue of the *Proceedings of the Society for Experimental Biology and Medicine*, pp. 43-46.

* References 26 through 29 (1936, 1938, 1939, 1944).

† References 35 through 39 (1938, 1939, 1941).

date. Oddly enough, only adult animals have been studied. When it was realized during the investigations that the neonatal-evoked cortical response to a physiological peripheral stimulus resembles the high-voltage "epileptic" spike discharge, and under conditions of barbiturate narcosis, the "spike-and-wave" complex seen most frequently in the EEG of the epileptic child, experiments were designed to investigate the epileptogenic properties of the developing cortex.

MATERIAL AND METHODS

The findings reported here were obtained on a series of 37 kittens up to 3 months of age and on 8 adult cats. The animals came from different litters, and there was variation in weight for a given age. Because the time of conception was unknown, the age is counted from the date of birth. Pentobarbital (Nembutal) or diallylbarbituric acid (Dial) was used in doses of from 2 to 5 mg. per 100 gm. of body weight, intraperitoneally, in the kittens and 50-75 mg. per kilogram in the cats. In the latter, in order to achieve deeper narcosis, additional amounts of pentobarbital were injected intravenously. The cortex was widely exposed over both hemispheres, and the responses of somatosensory and acoustic cortex were studied in all cases. The records were secured through wick electrodes led into an eight-channel Grass electroencephalograph or a two-beam oscilloscope operated by a high-gain Grass Preamplifier P-4. (The preamplifiers have a voltage gain of 80 db., flat from approximately 0.25 to 2000 cps.) In obtaining the latter, the beams were photographed with a Grass kymograph camera employing either a triggered sweep or a running film. Recording was obtained with both "bipolar" and "monopolar" techniques with a reference lead on the cut scalp. Except when otherwise stated, the tracings in the text are "monopolar" records, the upward deflection indicating negativity. Though records were always taken in both ways, most of the tracings presented in the text are "monopolar," because interpretation of records of the electrical responses of the cortex is much simpler with one localized lead and one "indifferent" lead (Eccles,[9] 1951). The auditory stimulus was a click produced by a 1-msec. square wave led into a Permaflex PDR 8 phone with a repetition rate of 0.5/sec. The instant of each application of the auditory stimulus was recorded in the EEG record by a signal-marking pen developed by Degelman[6] (1952). Surface-stimulating electrodes on the cortex were bipolar, with a separation of 3 mm. A Grass Stimulator Model 34 A with all parameters variable was used for electrocortical stimulation. Pentylenetetrazol (Metrazol) (10%) was applied topically (after drying the cortical area) or was given intraperitoneally (2%) in small doses, as required for the animal to reach the state of excitability necessary for the production of a sustained "after-discharge."

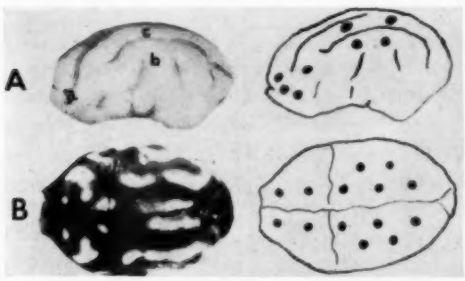


Fig. 1.—View of left hemisphere (*A*) and calvaria (*B*) with typical electrode placement on cortex and skull. (*a*) Sigmoid gyrus; (b) ectosylvian gyrus; (*c*) suprosylvian gyrus.

The usual experimental procedure consisted of the following steps: After the cortex was exposed and electrodes placed on various areas of both hemispheres, a search was made for an area of the somatosensory cortex that yielded the maximal potentials in response to tactual stimulation of the contralateral forepaw. This search was made by moving the wick electrode systematically over the cortex. The acoustic cortex (ectosylvian gyrus) was next explored in the same manner, using click stimuli. There were also two to three electrodes on the suprasylvian (association) cortex (Fig. 1*A*). The general outlines of the main sulci and gyri are usually sufficiently marked even in the first postnatal days that no difficulties were encountered in the identification of the cortical landmarks for the preliminary electrode placement. After identifying the points of maximal potential in the receiving areas, the form of the responses, their latency, and fatigability characteristics were studied both with the ink writer and with the oscilloscope. The influence of topical and systemic application of pentylenetetrazol was then studied. In the unanesthetized preparations, scalp incisions were made with use of local (0.5% procaine) anesthesia, the head was immobilized, and recording was made directly from several points on the skull. At early age, the calvaria is transparent, and one can locate the necessary landmarks, as shown in the photograph at the left of Figure 1*B*.

TERMINOLOGY

The following terms will be used to describe the different kinds of response observed: 1. The primary specific response. This is a response to an afferent volley sharply restricted to the "specific" cortical

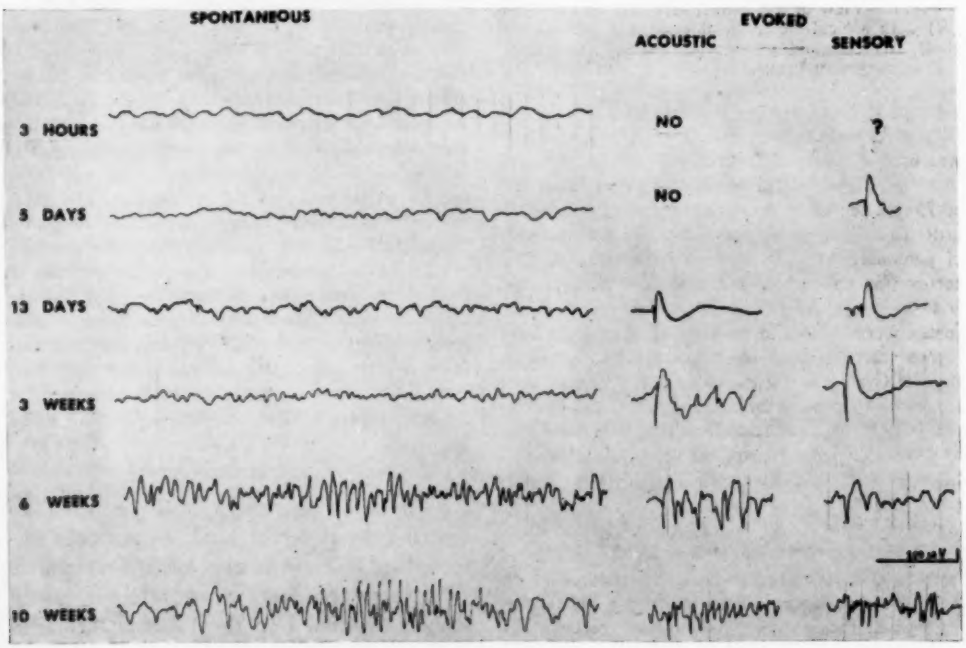
region. Its latency is 8 to 12 msec. 2. The secondary discharge. Unlike the primary response, the secondary discharge (*a*) is not restricted to the "specific" receiving cortical area but is widely distributed over both hemispheres, (*b*) is depressed at relatively slow rates of stimulation, and (*c*) has a long latency of 40 to 80 msec. 3. Repetitive after-discharge or response. Two types of repetitive after-discharge are now recognized: (*a*) the "fast" after-discharge (of Bremer) and (*b*) the "slow" after-discharge. The "fast" after-discharge, which may be as rapid as 60 waves per second, is most marked in the receiving areas and is depressed by barbiturate narcosis. The "slow" after-discharge (Chang,[4] 1950) is seen only when the brain is under the influence of barbiturates or of anoxia or in natural sleep (Bremer and Bonnet,[3] 1950). 4. Self-sustained after-discharge. This response represents in the adult animal the "tonic-clonic sequence" (Rosenblueth and Cannon,[34] 1942) and is an indirect cortical activity which follows the direct response of the cortex when the electrical stimulation is sufficiently intense to evoke it or when afferent physiological stimuli are combined with a convulsant drug, e. g., pentylenetetrazol. This activity, once started, is largely independent of the stimulus, tends to spread, and outlasts the periods of stimulation by some minutes. 5. "Spike-and-wave" discharge. The only criterion for using the term "spike and wave" in this study will be its descriptive meaning: A "spike-and-wave" discharge consists of a spike followed by a slow wave. This descriptive term is used here for all instances in which such a complex occurs, regardless of whether it is focal or generalized and whether it occurs as a single formation or in series. This parsimony is based on the results of the present study.

RESULTS

A. Form and Sequence of Emergence of Cortical Responses Under Barbiturate Anesthesia

Three hours after birth (Fig. 2) the spontaneous neocortical activity presents a mere base line sway. Evoked responses of the neocortex to physiological stimuli (sound

Fig. 2.—Samples of spontaneous and evoked neocortical electrical activity at various stages of postnatal development of the cat. Barbiturate anesthesia. Cortical recording.



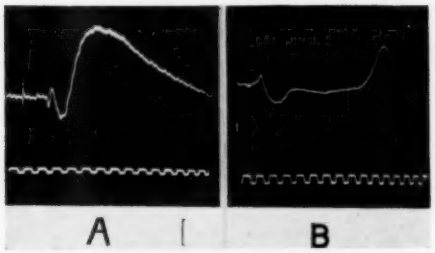


Fig. 3.—Oscilloscope tracing of "primary" response and "secondary" discharge (acoustic cortex). Note long latency and high-voltage slow wave at 13 days (*A*), reduced latency and voltage of "primary" response at 6 weeks (*B*), and long latency of "secondary response." Time base: 60 cycles per second. Vertical line: 100μv. Cortical recording: Sharp deflection indicates stimulus artifact.

and light) are absent. (An occasional response to touch could be obtained from the somatosensory cortex three hours postnatally and is, because of its inconsistency, classified as questionable.

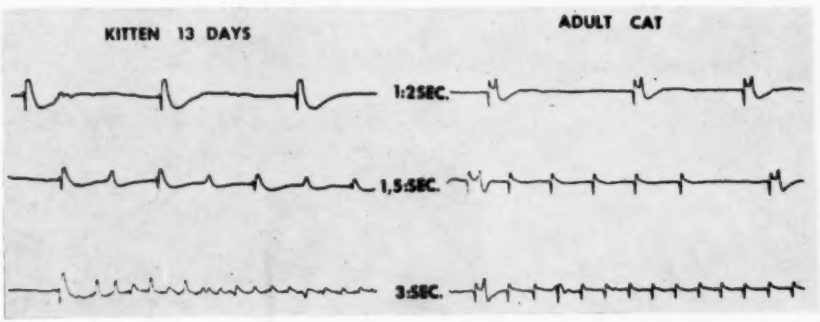
Five days postnatally the primary response of the somatosensory cortex is well established. Responses to tapping of the forepaws are elicited more consistently than those of the hindpaws. The responses are contralateral. The background rhythm at this age shows occasional poorly organized trains of 6- to 7-per-second oscillations.

At 13 days responses from the acoustic cortex are well developed and show much the same form as those of the somatosensory cortex. The primary response under barbiturate anesthesia at this stage of development has the following characteristics: (*a*) It is of a high voltage; (*b*) it consists of a spike followed by a large single slow wave; (*c*) it lacks an after-discharge; (*d*) it has a considerable latency (25-30 msec.) (Fig. 3*A*) and fatigability (Fig. 4). The oscilloscope tracing of the neonatal primary response (Fig. 3*A*), recorded from the cortex under conditions of moderate barbiturate depression, clearly demonstrates the large single slow wave that follows the triphasic spike response. The amplitude and duration (160 msec.) of this slow wave and the long latency of the spike differentiate the neonatal response from the adult type of response and the strychnine spikes. At three weeks and later the spontaneous activity has oscillations resembling spindle activity, and the primary responses are followed by secondary and occasional repetitive responses. At this time the latency of the primary response is substantially reduced (14-16 msec.). The emerging secondary discharge, however, has a considerable latency (Fig. 3*B*) (ca. 120 msec.). From 6 to 10 weeks the spontaneous activity shows more and more organized "barbiturate spindles"; the primary response is reduced in amplitude; its latency nears that of the adult, and the repetitive "slow" response is well developed.

B. Responses Recorded from the Skull in Unanesthetized Preparations

Because barbiturate narcosis in the adult cat alters the appearance of cortically evoked potentials, the question arose early in the

Fig. 4.—Form and fatigability characteristics of responses of acoustic cortex to single and repetitive stimulation (clicks) in a 13-day-old kitten and adult cat. Note large slow wave following single responses and blocking of the "positive" component at higher rates of stimulation (kitten). Cortical recording.



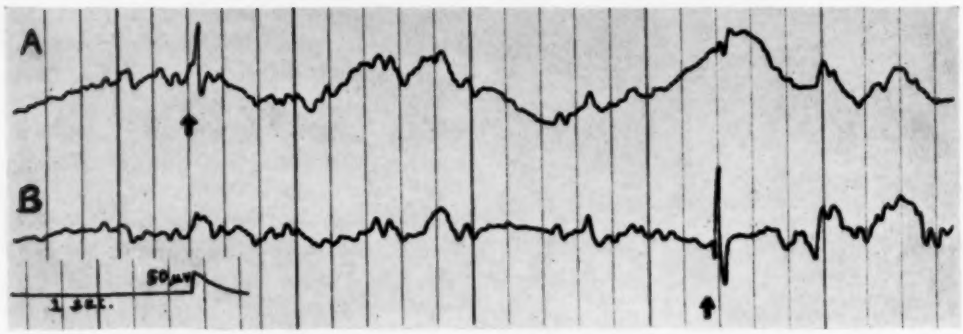
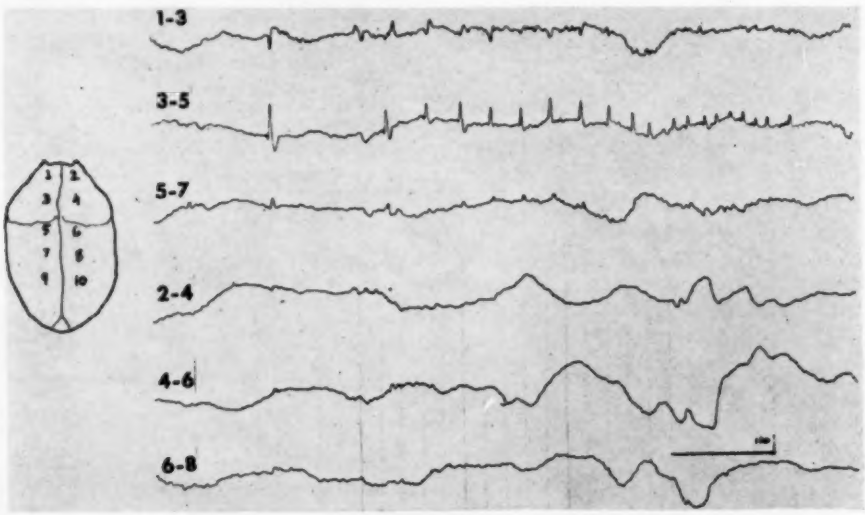


Fig. 5.—Responses to single tap to right (*A*) and left (*B*) forepaw in a 5-day-old, unanesthetized kitten. Monopolar recording from left (*A*) and right (*B*) frontal aspects of the skull.

investigation how many of the unusual features of the neonatal activity are a result of the narcotic action. Data were thus collected from experiments performed on unanesthetized animals of various ages. In contrast to the adult animals, in which the specific "primary" response becomes evident when the cortex is rendered quiescent by deep narcosis, it was found that in the young animal high-voltage responses could be recorded from the skull without use of depressive agents. Figure 5 illustrates responses to tapping the right and the left forepaw as recorded in succession from the skull of a nonanesthetized 5-day-old kitten. A better localization of this "spike" response was obtained by using a bipolar hook-up, as seen in Figure 6. Here, the tap on the right forepaw was applied with an increasing frequency, from 1 to 7 per second. It is evident from the phase reversal at electrode 3 that the response is confined to the contralateral anterior aspects of the skull overlying the somatosensory cortex. Like those recorded on the cortex of an anesthetized animal of comparable age, the responses in Figures 5 and 6 consist of high-voltage single spikes without a repetitive response. The triphasicity of the spike, especially to single taps, is brought out very clearly in the unanesthetized animal, whereas the slow wave recorded from the cortex under

Fig. 6.—Responses to single and repetitive tapping of right forepaw in a 5-day-old, unanesthetized kitten. Push-pull recording from skull.



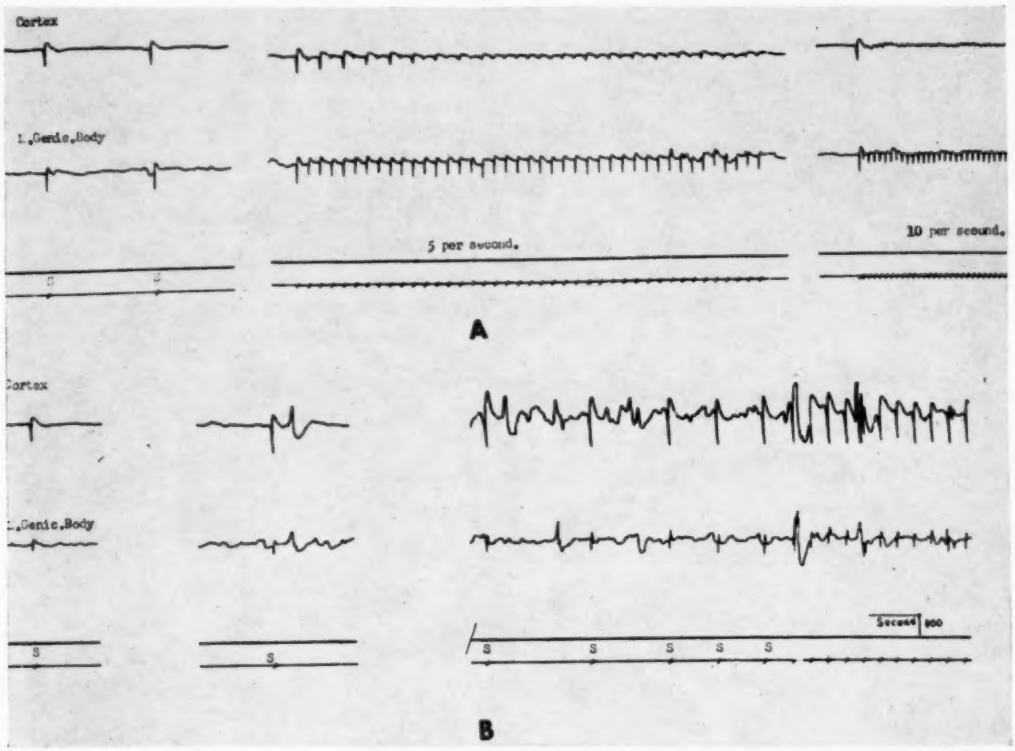


Fig. 7.—Electrical tracings obtained during deep pentobarbital (Nembutal) narcosis from the acoustic cortex and medial geniculate body. *A*, before, and *B*, after, the application of pentylenetetrazol (Metrazol). *S*, stimulus.

anesthesia, and described previously, is less marked or completely absent.

C. The Secondary Discharge

The secondary discharge appears in kittens at a later ontogenetical stage than the primary response. Because in this investigation the secondary discharge was studied with click stimuli, while the original description by Forbes and Morison [12] (1939) relates to electrical events following sciatic stimulation, data obtained on adult cats are reported here for comparison. In deep barbiturate narcosis (Fig. 4, adult cat) the primary acoustic response has an initial surface-positive spike, followed by a smaller negative phase. The secondary discharge then occurs if the rate of stimulation is low. At higher frequencies (1.5/sec.) the first stimulus evoked a secondary discharge, the others only primary responses. During very deep narcosis (Fig. 7*A*) the secondary discharge disappears completely; the "primary" responses diminish in voltage and follow only relatively low stimulation rates. The records in Figure 7 were obtained from the right acoustic cortex and the right medial geniculate body (depth electrode) of an adult cat in very deep pentobarbital anesthesia. In Figure 7*A* the primary responses from the acoustic cortex fatigue easily, alternating and waning with a stimulation rate of but 5 per second. At a rate of 10 per second only the first cortical response is recorded, though the responses of the medial geniculate body to the same stimulus follow it perfectly. For comparison, a study was made on the influence of a convulsant (pentylenetetrazol) on the primary acoustic responses from the same two places. To obtain Figure 7*B*, increasing doses of pentylenetetrazol were injected intravenously to cause a progressive increase in voltage of

the surface-positive cortical spike with little or no change in the spike recorded in the medial geniculate body.

D. Influence of Convulsant Agents on the Neonatal Cortex

Though single "spike-and-wave" complexes were obtained from the normal cortex of our young animals, no sustained repetition of such discharges or true epileptic after-discharge was ever observed. In order to produce such an after-discharge, a convulsant pentylenetetrazol or direct electrocortical stimulation had to be used.

1. Pentylenetetrazol activation combined with sensory stimulation (anesthetized preparation). If pentylentetrazol (10%) is applied to the exposed sensory cortex of a 2- to 3-week-old kitten (or a subconvulsant dose of pentylenetetrazol is given intraperitoneally), tapping of a forepaw evokes high-voltage spike-and-wave complexes in the contralateral sensory cortex. If, after a few seconds of stimulation, the stimulus is withheld, a rhythmic self-sustained, and occasionally propagated, after-discharge will follow and lasts from 5 to 10 minutes. If propagation occurs, the after-discharge will creep along the cortex to neighboring regions of the hemisphere (Fig. 8) to the acoustic and association (surprasylvian) gyrus. The after-discharge resembles single evoked responses in form and consists of a high-voltage, usually triphasic spike, followed by a slow wave, repeated at about 2 to 2.5 per second. In the suprasylvian association area the "spike-and-wave" response is less well developed. There is no admixture of fast trains of spikes. Their absence, we believe, is of fundamental significance in any after-discharge produced in the immature cortex. At this stage of development, if a spread occurs, it is confined to the hemisphere contralateral to the stimulated paw. The spread may be very slow, 9 to 10 mm. per minute. The same kind of after-discharge is observed from auditory stimulation, except that convulsive activity then starts from the specific acoustic cortex. At 6 weeks of age the seizure spreads faster and involves both hemispheres.

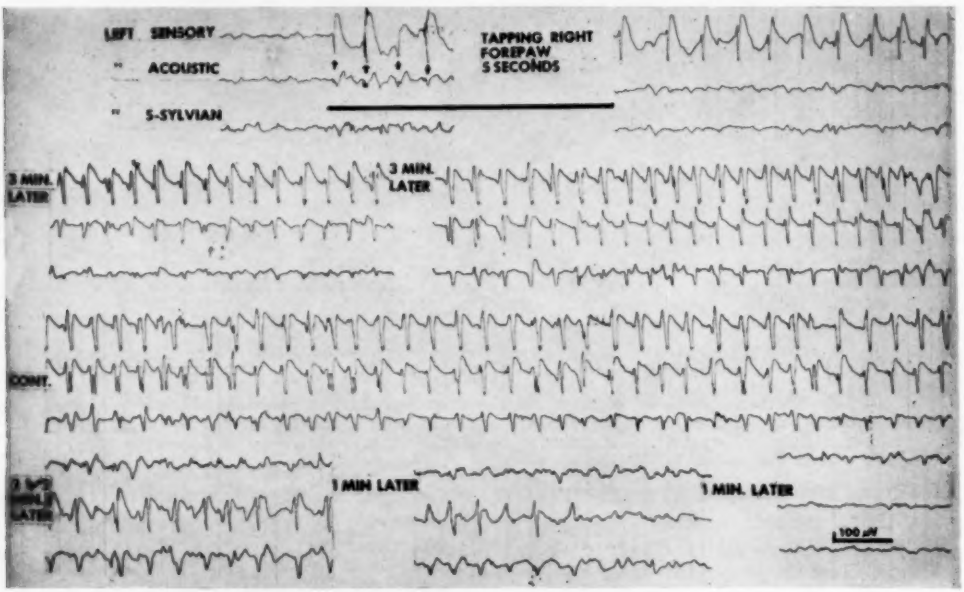


Fig. 8.—Focal, "spike-and-wave," self-sustained after-discharge evoked in the left sensory cortex of a 3-week-old kitten. Note spread of seizure activity to suprasylvian and acoustic cortex. Barbiturate anesthesia. Heavy line indicates duration of stimulation (tapping of right forepaw). Cortical recording.

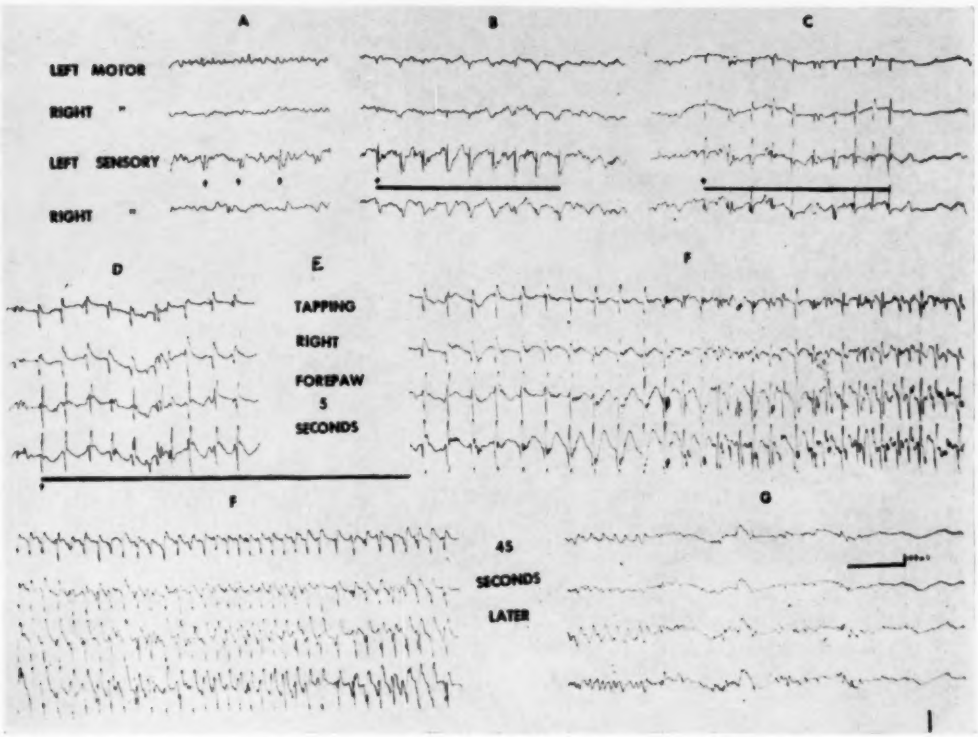


Fig. 9.—Seizure discharges evoked in a 12-week-old kitten by tapping of right forepaw. (*A*) Before injection of pentylenetetrazol; (*B-C* and *D*) gradual increase in dose of injected pentylenetetrazol in order to produce generalization of seizure discharges (*F*). Pentobarbital anesthesia. Cortical recording.

Rapid trains of spikes are still missing. It is only in animals (Fig. 9) older than 6 weeks that the high-voltage fast activity (rapid spikes) makes its appearance. The fast activity is, of course, easiest to produce in the adult cortex, when the self-sustained after-discharge shows very fast high-amplitude spikes (tonic phase), followed by rhythmic spikes of a slower frequency (clonic phase).

2. Direct electrical stimulation of the neonatal cortex. The after-discharge of the neonatal cortex induced by direct electrical stimulation takes different forms, depending on the age and the area stimulated. Thus, as seen in Figure 10*A*, the ontogenetically earliest after-discharge consists of irregular slow waves with only a slight suggestion of sharp waves. Such a pattern has been obtained from the primary acoustic cortex in the first (two to four) days of postnatal life, as well as somewhat later (six to eight days) from the posterior suprasylvian cortex. The pattern seen in Figure 10*B* shows the type of after-discharge recorded from the suprasylvian gyrus at 13 days and consists of spikes, followed by large smooth slow waves at 1- to 1.5-per-second frequency. At this time records from the more developed specific cortex (Fig. 10*C*) contain faster "spike-and-wave" discharges, at a rate of approximately 2.5 per second. With increasing age, trains of fast spikes (Figs. 10*D*) emerge. The latter become a constant feature of any after-discharge evoked in the normal adult cortex.

Figures 10, 11, and 12 exhibit the essential difference in the shape and repetition rate of the various components of the after-discharge in kittens and cats. The adult after-discharge contains all the components (fast and slow) that have emerged gradually during development. The immature cortex discharges at a

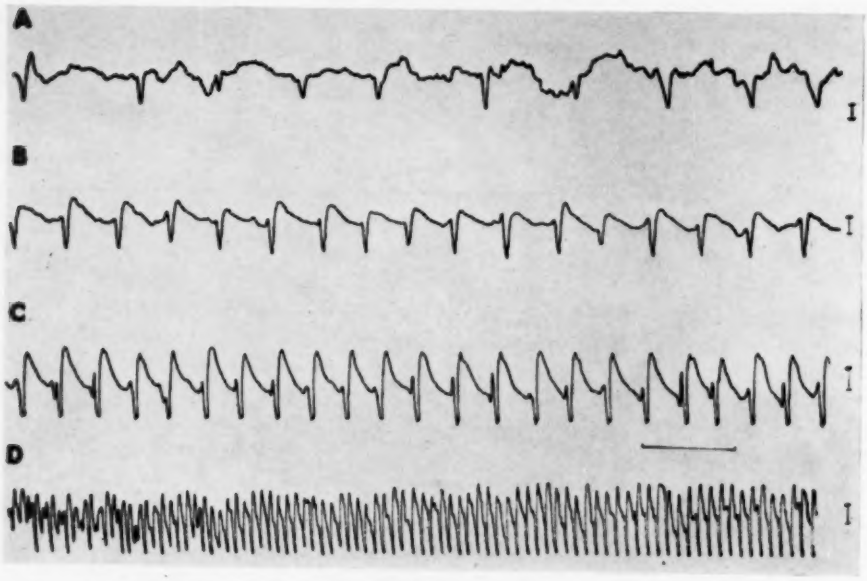
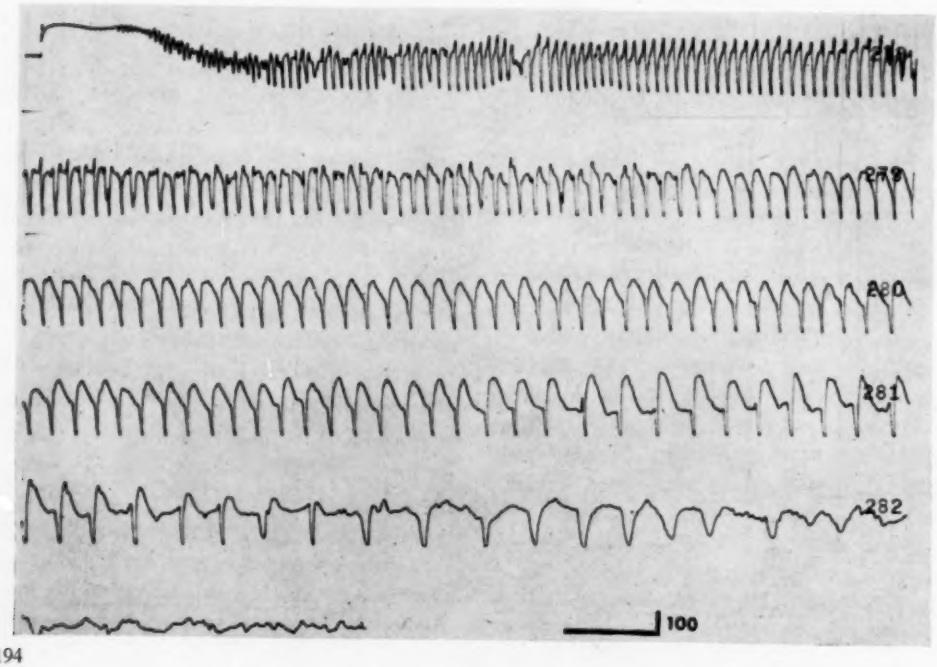


Fig. 10.—Forms of epileptic after-discharges induced at various stages of maturation: (*A*) Posterior suprasylvian gyrus (6 days); (*B*) anterior suprasylvian gyrus (13 days); (*C*) acoustic cortex (13 days); (*D*) acoustic cortex. Adult cat, weight 2.15 kg.

Fig. 11.—Continuous tracing of a self-sustained after-discharge following electrical stimulation of cortex of adult cat.



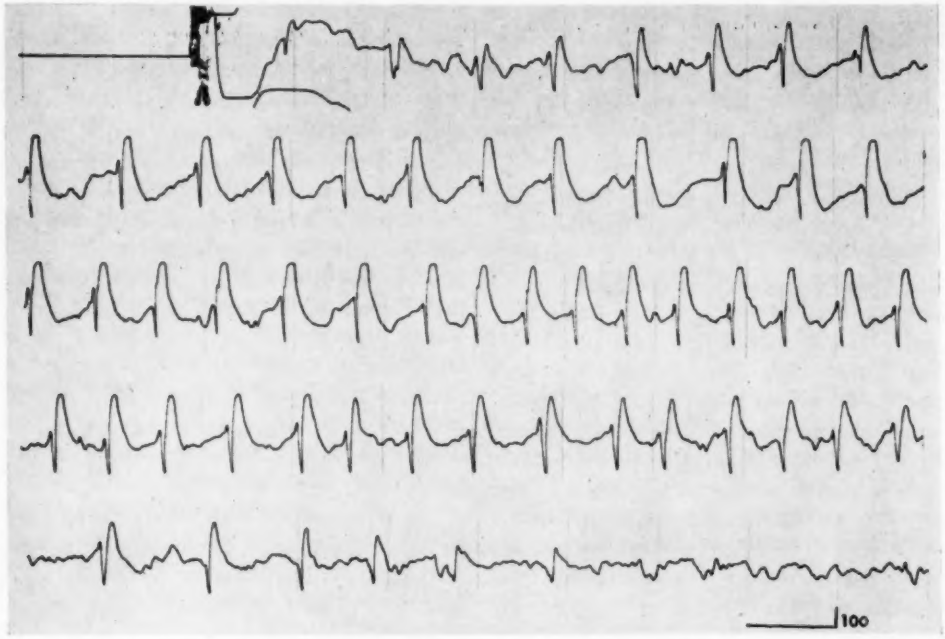
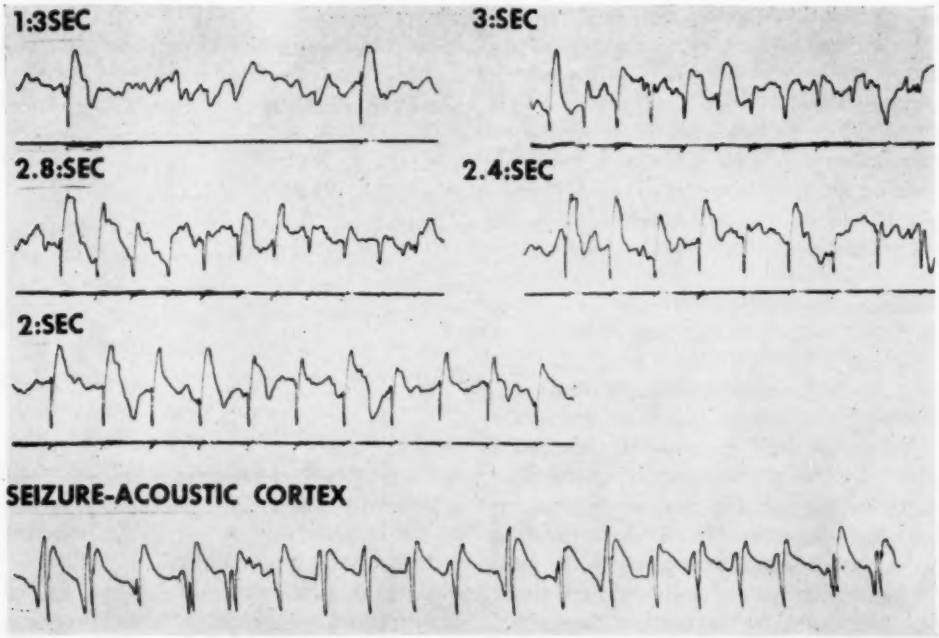


Fig. 12.—Self-sustained epileptic after-discharge following electrical stimulation of acoustic cortex of a 13-day-old kitten.

Fig. 13.—Samples of responses to auditory stimuli obtained at different rates of stimulation and their relation to induced self-sustained seizure activity in 3-week-old kitten.



slower rate, and, depending on the age, records contain (1) slow waves, (2) "slow spikes and waves" or (3) fast "spikes and waves." The rapid trains of spikes are still missing and have yet to appear in development.

E. Relationship of Frequency of "Spike-and-Wave" After-Discharge to the Excitability Characteristic of the Immature Cortex

In order to gain more understanding of the mechanism of the "spike-and-wave" frequency (a point of considerable clinical interest), the following experiment was performed. In a 3-week-old kitten the "fatigability" characteristics of the acoustic cortex were tested by the application of intermittent auditory stimuli at various frequencies. The responses of the acoustic cortex to stimuli within the 2- to 3-per-second range are shown in Figure 13. It is seen that the critical maximal frequency the cortex could follow without a decrease in amplitude is 2 per second. After this was established, a 10% solution of pentylenetetrazol was applied topically to the sensory cortex. The contralateral foreleg was then stimulated by tapping and a "spike-and-wave" after-discharge produced in the pentylenetetrazol-sensitized sensory cortex. After the after-discharge invaded the acoustic cortex, it could be shown that the self-sustained seizure frequency of the acoustic cortex was 2 per second. This suggests that the frequency of the discharge is an inherent property of the cortex and depends on the state of maturation and "fatigability," rather than on the rate of stimulus, or pacemaker.

COMMENT

A. Physiological Aspects of Electro-Ontogenesis

As shown above, postnatal development of the electrical activity of the neocortex of the cat follows a definite temporal and spatial order. 1. The primary receiving areas of the neocortex are the first to respond to physiological sensory stimuli. 2. The earliest cortical response gradually assumes the form of a high-voltage spike (followed by a single large negative slow wave when the animal is under barbiturate anesthesia). 3. The secondary and repetitive responses appear later. With the appearance of the latter, the primary spike undergoes a substantial reduction in amplitude.

An interesting feature of the "primary" response at an early ontogenetical stage is its form of a simple spike in the unanesthetized animal and a "spike-and-wave" complex in the anesthetized animal. Whether in the form of a "spike" or a "spike-and-wave," this type of response seems to be ontogenetically the "primordial" pattern of electrical activity evoked by a physiological stimulus at a stage of development when incoming volleys to the cortex are limited to the primary specific areas.

The "secondary" and "repetitive" responses represent, as it is commonly agreed (Eccles,[9] 1951; French, Verzeano, and Magoun,[13] 1953), polysynaptic phenomena. Their lack in early postnatal life is most probably a result of the lack of cortical interneuronal connections. Whatever the origin, an absence of the repetitive "slow" and "fast" after-discharge seems to indicate a low level of cortical development. With progressing age the addition of these components of the cortical response goes parallel with a decrease in amplitude of the initial primary spike and the slow wave. In other words, a more complex and differentiated response of lower voltage develops from a simple massive, high-voltage discharge. (This electrical characteristic of "maturation" is not invalidated by the possible effects of narcosis, as was shown on the unanesthetized preparations with electrical recording from the skull. The latter technique excludes both the action of narcosis and the possible effects of artificial conditions if the cortex is exposed to air.)

The sequence of neocortical participation in the elaboration of sensory impulses in cats begins with the somesthetic area, followed by the acoustic and visual. This, together with the earlier appearance of cortical responses to stimulation of the forelegs, as compared with the hindlegs, is in agreement

with the known order of development of behavior. It also complements physiologically the anatomical findings of Conel [5] (1947). After comparing the cortex of a 3-month-old with that of a 1-month-old infant, Conel reported that the cortex in the somesthetic area is more advanced in development than the cortex in either the visual area or the acoustic area. There is, further, a difference in degree of development within this area, in that the functional regions for the upper trunk, shoulder, arm, forearm, and hand are more advanced in development than the regions for the head and lower extremity.

The finding that the "secondary discharge" is of later ontogenetical origin than the "primary" response throws more light on the genesis of the recently discovered "secondary sensory system."

There is now a good deal of evidence that, apart from the classical oligosynaptic pathways (lateral lemniscus, thalamic relay nucleus, and specific receiving cortex) involving transmission of the primary response, there is a supplementary, polysynaptic route subserving the transmission of the "secondary" discharge. The latter, diffusely distributed over both hemispheres, has been considered to reach the cortex through the medial brain system (Dempsey, Morison, and Morison,[7] 1941). It was shown by French, Verzeano, and Magoun [13] that the features concerning the course and distribution of the "secondary discharge" resemble closely those shown to subserve the "arousal response" to afferent stimulation. It had been previously demonstrated (Starzl, Taylor, and Magoun,[40] 1951) that sensory impulses reach the centrencephalic brain stem presumably through fibers from the lateral pathways and that potentials evoked by stimulation of this central region are distributed diffusely over the cortex. The stimulation of this central region by peripheral sensory impulses causes arousal of a sleeping animal. The area has therefore been called the reticular activating system (Moruzzi and Magoun,[32] 1949). The functional significance of the two parallel sensory systems has been recently discussed by French, Verzeano, and Magoun.[13] They conclude that information delivered over the lateral system is essential for the perception and recognition of stimuli and their localization and serves also in the discrimination of sensory modality. The medial, or "secondary," system, on the other hand, provides the maintenance and initiation of the conscious state, "without which no integrated sensory, motor or adaptive function is possible."

In the light of my findings, it seems pertinent to point out that the diffuse activation of the neocortex by peripheral sensory stimuli is a slowly developing function of the brain. On the other side, the ability of arousal from sleep (crude wakefulness) is found immediately after birth. Such an arousal subserves very primitive behavior and most probably is confined to lower, subcortical, mechanisms. Only with progressing age and emergence of mechanisms capable of diffuse activation of the whole cortex, as well as the subcortex, will arousal be associated not with crude "wakefulness" alone but also with the readiness to execute the integrated functions of the mature cerebral cortex.

The findings seem therefore to provide some physiological evidence for the differentiation of two parts of the activation system: (1) a mechanism for primitive "wakefulness," not requiring cortical participation (decorticated animal, the newborn), and (2) a mechanism capable of maintaining the "conscious" state, in which integrated motor, sensory, or adaptive function is possible. The latter mechanism, though certainly dependent, and probably superimposed, on the former (though not vice versa), develops slowly with increasing maturation and differentiation of the cortex and its connections with subcortical structures. Electro-ontogenetic studies enabling us to follow the course of functional maturation of electrical concomitants of cortical "activation" may give us in the future a greater insight in this matter. From the evidence presented here, however, the view of a purely subcortical "seat of consciousness" (a view based largely on findings that "consciousness" is lost with

subcortical lesions only) takes into consideration the anatomy and function of the ontogenetically older, subcortical part of the activating system, which is a part subserving crude "wakefulness" rather than the "highest state of differentiation" (Hughlings Jackson,[21] 1931). Should one try to localize the latter, one would have to consider the ontogenetically younger part of the system, which embraces principally, though not exclusively, the vast territory of the cerebral cortex.

B. Ontogenetic Aspects of the Epileptic After-Discharge

The method of investigation of the epileptic properties of the cortex by studying the after-effects of direct electrical stimulation or by peripheral sensory stimulation combined with pentylenetetrazol sensitization has been extensively studied by several investigators. The effect on the EEG has been described, among others, by Dusser de Barenne and McCulloch[8] (1938), Rosenblueth and Cannon,[24] and Gastaut and Hunter[14] (1950).

Rosenblueth and Cannon, in an extensive study performed on adult animals, described a variety of patterns obtained during an after-discharge induced in various areas of the cortex. As found by these investigators, once the threshold of stimulation has been reached, the self-sustained activity begins, and it begins with fast waves. This stage may or may not be followed by subsequent slower components.

The results of investigations in young animals make it more comprehensible why previous attempts by many investigators to reproduce the "spike-and-wave" component of the self-sustained after-discharge in pure form (without being preceded or followed by "fast" activity) were unsuccessful. The explanation appears to lie in the fact that these investigators have been working exclusively on adult animals. So it was reported (Jasper and Droogleever-Fortuyn,[22] 1947) that stimulation of the medial thalamic structures may result in a "spike-and-wave" activity of large areas of the cortex. This activity was dependent on a stimulus frequency of about 3 per second. Gastaut and Hunter[14] (1950) found that, with pentylenetetrazol sensitization and photic stimulation, repeated stimuli applied with a frequency of about 3 per second produce "spike-and-wave" formations in the cortex. However, the "spike-and-wave" discharges lasted only as long as the stimulation and have not been produced as a consistent self-maintained seizure activity after the withdrawal of the stimulus (Gastaut ‡). If a self-sustained discharge occurred, it consisted of, or was followed by, fast spikes of the type seen during the tonic phase of a grand mal seizure.

The principles of development of the electrocorticogram of the cat indicate an inability of the immature cortex to produce fast frequencies. This physiological characteristic of immaturity is also manifesting itself during the pathological state, in the epileptic after-discharge. As shown above (Figure 10), the ontogenetic development of the epileptic after-discharge proceeds from (1) irregular slow waves, (2) slow "spikes and waves," (3) fast "spikes and waves" to (4) fast spikes. For this reason, all other variables being equal, the induced cortical epileptic pattern in the normal cortex will include any or all of these components, depending upon the age of the animal and the cortical area stimulated. Areal differences are particularly important in the young because "maturation" of both the physiological response and the epileptic after-discharge have a different time course in different areas. The primary receiving areas may show fast spikes at a time when the "association" areas show "spikes and waves" only. Whether the differences in the types of after-discharge obtained from direct stimulation of the developing cortex can be ascribed to "maturation" is certainly only an inference. However, the evidence presented here seems to point in this direction, and it is reasonable to assume that no factor other than "maturation" could account for the progressive electrical changes observed in the growing cortex. It is, therefore, reasonable to assume

‡ Personal communication to the author (1953).

that the change in the physiological electrical response and the appearance of fast spikes in the self-sustained after-discharge are due to activity of neuronal elements maturing at a later time. The different type of epileptic discharge ("spikes and waves" and fast spikes) may therefore be assumed to be attributable to different neuronal systems that belong to different ontogenetical levels. This concept is in line with conclusions of Rosenblueth and Cannon,[34] who observed that the different components of the epileptic cortical after-discharge depend on activity of different neuronal cortical elements. In the case of adult cortex the appearance of one or the other component will depend on whether the threshold for a particular neuronal system has been reached. If the stimulus is applied directly to the adult cortex, the epileptic after-discharge will show initially the fast spikes and will be followed by other components, depending upon whether "the subsequent set of elements has been thrown into activity" (Rosenblueth and Cannon[34]). When, however, the convulsant agent is mediated through the blood stream (slow intravenous injection of pentylenetetrazol), the seizure pattern may consist initially of "spikes and waves" and then be followed by fast spikes. This fractionation of convulsive activity in adult cortex (in both man and beast) can be accounted for by the existence of different thresholds to pentylenetetrazol for different neuronal systems, a view also subscribed to by Ziskind, Bercel, and Friedman[42] (1947) in their attempt to explain the form of preconvulsive changes in the EEG after pentylenetetrazol injection.

The observations made in this study seem to warrant the formulation of an ontogenetical concept of seizure discharges. Though fully aware of its largely hypothetical character, I am convinced of the usefulness of such a concept, since it offers a lead hitherto largely neglected in experimental electrophysiology. It also seems to provide a parsimonious and unitary explanation of the origin of various forms of seizure discharges.

Anatomical studies on cortical maturation (Conel[5]) show that not only do various neocortical areas develop at different times but neuronal elements within each area have a developmental sequence of their own. Thus, the deeper layers and the larger cells mature earlier than the superficial layers and smaller neurons. This maturational differentiation of neuronal elements is reflected by the variable increase in width of each particular area; this, for the most part, is related to the growth of dendritic arborization, increase in myelin, and formation of new interneuronal connections. The "evolution" of neocortical function proceeds, therefore, not only longitudinally, from area to area (primary to secondary "association areas") but also transversely, from the deeper layers up. Local "dissolution" of cortical function is likely, therefore, to show the same "direction" in reverse.

There is now good evidence that an epileptic focus is objectively, as well as physiologically, abnormal. Histologically, the epileptogenic area shows local destruction in minute cellular areas (Alexander and Putnam,[1] 1938; Penfield and Humphreys[33]) of the thinned cortex and islands of gray matter, caused by vascular changes. This *partially* damaged cortex serves as a focus for epileptic discharges. It is feasible to assume that local, pathological events leading to an epileptic focus will permanently or temporarily eliminate the more vulnerable, ontogenetically later-maturing, elements and (anatomically or functionally) reduce the affected area to an early developmental status. Continuous or episodic, local or systemic metabolic impairment acting upon such an area will cause abnormal stimulation of neural elements whose electrical output will necessarily have the form and frequency characteristics of immature cortex, with its high-voltage and slow-frequency discharges. The random firing of an epileptic focus in the interseizure EEG will, therefore, show the forms of discharge seen in the normal infantile cortex under conditions of stimulation ("spikes and spike-waves"), depending on how severe is the "dissolution" or the partial damage in the epileptogenic area. However, a spread from this area, during a fit, to nor-

mal cortex will produce a "normal" after-discharge, with the "tonic-clonic" sequence characteristic of the adult cortex (rapid spikes followed by spike-waves). The form of discharge of an epileptogenic area will thus depend on the ontogenetical level to which the discharging elements belong.

"Spike-and-wave" discharges of various frequencies depend on activity of neuronal elements which mature before those responsible for the fast spikes. The low-frequency repetition rate of this type of epileptic discharge (up to 3.5 per second) is an inherent characteristic of an ontogenetically older neuronal system and is independent of the rate of stimulation which triggers the self-sustained seizure discharges. Depending on circumstances within the cortex, this type of seizure discharge will appear focally or bilaterally, at a slower or somewhat faster rate, as a slow (1- to 2-per-second) spike and wave (petit mal variant of Gibbs, Gibbs, and Lennox,[15] 1939) or as a 2.5- to 3.5-per-second (petit mal) spike and wave. The occurrence of the focal type of all these discharges is possible in both the immature and the adult brain. In the young there will obviously be a somewhat greater tendency to this pattern than in the adult, because in the former pathology will be combined with immaturity. The generalized "slow spikes and waves" and "3-per-second spikes and waves," however, are predominantly a pattern of childhood, because maturational, as well as pathophysiological, factors of a general, and not focal, nature are a prerequisite. The generalization of this type of discharge suggests that an ontogenetically older system alone is thrown synchronously into epileptic activity. In the case of the generalized slow "spike-and-wave" (petit mal variant) discharges, some maturational impairment and increased neuronal fatigability are suggested by the bluntness of the spike and the slower rate of discharge. However, in the case of true "petit mal," the assumption can be made that a normally developed "older" system is discharging with its inherent frequency and form.

This concept seems also to be able to account for some clinical and electroencephalographic features of epilepsy previously unexplainable. The predominant occurrence of petit mal in the young, its occasional transition into grand mal at a later age, the interrelationship and mutual antagonism of both forms of epilepsy, and the difference in sensitivity to drugs and CO_2 blood levels are more comprehensible if two different neuronal systems are taken into consideration. The difference in the age of onset of petit mal and grand mal and the occasional transition of the former into the latter are explained by the difference in the time of maturation of the two systems. In cases in which petit mal seizures persist and both types of fits occur at a later age, different seizure thresholds of the two systems can explain the observation that control of one type of seizure may increase the frequency of the other type. The selective sensitivity to anticonvulsant drugs and CO_2 blood levels may also be related to the physiological differences in the metabolism of the two ontogenetically different systems. Finally, the findings seem to cast some light on the question whether all seizure discharges seen in clinical electroencephalography are "abnormal." There are indications from this study that only self-sustained epileptic after-discharges are unequivocally "unphysiological" and alien to normal cerebral activity, since they are not found, under physiological conditions, at any stage of ontogenetical development. However, not unlike the Babinski reflex, single "seizure discharges" are physiological at certain early stages of development. Probably, in clinical evaluation as to normalcy or abnormalcy of such single discharges, due consideration should be given to other variables, of which the most important is age (maturation).

SUMMARY

Studies on the ontogenesis of the cat's electrocorticogram reveal a definite temporal and spatial order. In the kitten the first signs of evoked electrical activity of the neocortex appear in the primary receiving areas. The somatosensory cortex shows activity at

an earlier postnatal age than the auditory and visual areas. The evoked neocortical response to physiological sensory stimuli consists (under conditions of barbiturate anesthesia) of a single high-voltage spike-and-wave complex. The secondary discharge and the repetitive response are of later ontogenetical origin. With the appearance of the latter potentials (and with progressive age) the voltage and latency of the primary spike response both undergo a steady reduction. At a certain, early state the induced and self-sustained epileptic after-discharge of the cortex consists of spike-and-wave complexes without admixture of fast spikes, the latter being of later ontogenetical origin. The difficulties experienced by previous investigators who attempted to reproduce in adult animals consistent, self-sustained spike-and-wave discharges may be obviated by using immature animals. The experimental and clinical significance of the findings are discussed and a unitary, ontogenetical concept of seizure discharges is proposed.

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Multiple Sclerosis and the Local Weather

A Four-Year Study of Correlation Between Multiple Sclerosis Exacerbation and Local Weather Factors in Montreal

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The difficulties of linking physiological changes in people with weather factors are great. They are increased manyfold when the study is limited to the macroclimate of the approximate geographic environs of a person or group of persons, since the physiological interactions are with the microclimate in immediate contact with the person, rather than with the geographic weather. The macroclimate is considerably modified by factors such as buildings, clothing, activity, etc.

The influence of weather on multiple sclerosis has been the subject of frequent discussions. Many writers have expressed the thought that the disease is influenced by climate factors, and Ziegler [1] reported that exacerbations of the disease in Minnesota occurred most frequently in the spring. Limburg [2] was unable to find statistical evidence to support this contention but felt that his studies supported previous observations that the disease is more frequent in colder climates. He suggested, on the basis of mortality statistics, that below an isotherm of 60 F the disease is much more frequent than in areas with an isotherm above this level. The studies of Kurland and collaborators * in general confirm the observations of Limburg. Kurland stated [4] that these observations tend to indicate that the geographic-latitude differences in incidence of multiple sclerosis are due to differences in exposure to external causative factors. Other studies (Swank and collaborators †) support this general thesis, but also seem to indicate that the variations in incidence are related to differences in the amount of fat intake of the general population—a high incidence of multiple sclerosis is related to a high-fat intake; a low incidence, to a low-fat intake.

In previous papers ‡ it was reported that in the Montreal area most exacerbations of multiple sclerosis seemed to occur during periods of changeable weather in January, and again in the April-May period. The present study undertakes to find out whether this is true, and to determine if possible what specific climate factors significantly influence the course of the disease. This has been done by using clinical histories of a large group of multiple sclerosis patients observed over a period of six years at the Montreal Neurological Institute and relating the exacerbations of the disease to various components of the local weather.

MATERIALS

The patients were interviewed every one to two months by one of us (R. L. S.), and all evidences of activity of the disease were recorded. Only patients with clear-cut exacerbations who were able to date the onset of their exacerbations accurately were used in the weather study. Many of these patients had two or more exacerbations during the four-year observation period from January, 1950, through November, 1953. The group of patients thus suitable for study was limited in size, numbering 17 at the beginning of this period and 51 at the end. All weather data were obtained from the McGill University Observatory, Dorval Air-

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* References 3 and 4.

† References 5 and 6.

‡ References 7 and 8.

port, and Water Resources Division, Department of Mines and Natural Resources, Ottawa, Ont., Canada.

Most of the patients were on a low-fat diet,[7] but some either broke diet or for various reasons had never been placed on the diet. Of 137 exacerbations observed during the period, 41 occurred in patients not on low-fat diet at the time and 96 in patients on the low-fat diet. The specific effect of the low-fat diet, which appears simply to lengthen the interval between exacerbations, is the subject of other reports.§ Diet as such is one of many intervening variables that are ignored in this study of gross correlation between weather factors and multiple sclerosis exacerbations.

TABLE 1.—*Distribution of Multiple Sclerosis Episodes over the Twelve Months for a Four-Year Period*

Month	Patient-Months at Risk	Observed Episodes	Expected	χ^2	
January	142	15	10.4	2.03	
February	147	12	10.8	0.13	
March	147	8	10.8	0.72	
April	158	16	11.2	2.13	
May	158	13	11.6	0.17	
June	162	14	11.9	0.37	
July	162	8	11.9	1.28	
August	163	6	12.0	3.00	
September	167	13	12.3	0.04	
October	170	16	12.5	1.04	
November	171	11	12.6	0.18	
December	123	5	9.0	1.77	
Total	1,865	137	137.0	12.86	$P = 0.30$

STATISTICAL ANALYSIS

The observations collected over this period were systematically recorded. Although they were quantitatively scanty for supporting any very complex analysis, their high quality nevertheless suggested the possibility of detecting specific weather determination if strongly present. If no correlation were to be detected by these data, one could at least conclude that weather factors are of negligible importance in multiple sclerosis.

The first test applied to the data was one designed to examine whether there was any gross tendency for multiple sclerosis episodes to be concentrated in some months more than in others. The four-year experience produced 137 episodes in 1865 patient-months at risk, for a rate of 0.0735 episode per patient-month, or 0.88 episode per patient-year. On the hypothesis of no seasonal influence, we should expect these episodes to be spread evenly, except for chance deviations, over the 12 months.

The values obtained by adding together the 4-year data for each of the 12 months are presented in Table 1.

§ References 7 and 8.

The χ^2 values are a measure of the discrepancies between the numbers of episodes observed and those expected on the hypothesis of no month-to-month differences in episode rate. The χ^2 value for a single month would be as high as 3.00 about 10% of the time by chance alone, and this occurs once in 12 months. So, although our suspicions may be aroused, we cannot take at face value the apparent suggestion that August is a favorable month for multiple sclerosis sufferers. The next most discrepant month (January) shows no more deviation from expectation than chance would produce about 15% of the time. Adding all the months together for a total χ^2 value of 12.86, with 11 degrees of freedom, we ascertain that in general there is no reason to believe that one month is any better or any worse than another for multiple sclerosis episodes, since the chance probability of this large a χ^2 value is about 0.30. Our findings, when taken by months, do not support the gross clinical impression that multiple sclerosis episodes are more frequent during the month of January or in the spring, or in any other particular month.

The calendar month, however, is a rather long period for weather changes and may tend to smooth them out unduly. It was decided, therefore, to seek correlations on the finer scale of day-to-day weather factors for shorter periods, say, 5 to 10 days.

Two immediate problems were choice of weather factors and choice of time interval. The following weather factors were easily available:

Temperature: Daily maximum, minimum, and mean

Humidity, relative: Daily mean

Sunshine: Daily percentage of possible sunshine

Wind velocity: Daily mean

Solar radiation: Daily total

River run-off: Daily total of Ottawa River

Precipitation, barometric pressure, and atmospheric inversions were not included in the study.

Preliminary graphic analysis suggested that temperature factors would be most likely to show correlation with multiple sclerosis episodes and that change in temperature, rather than level, might be the determining factor. The other weather factors all interact, however, with temperature; so it was felt worth while to explore their contributions as well, separately and in combination.

A time period of 10 days was chosen for the analysis. It was thought that if weather factors were influencing multiple sclerosis, this influence would certainly be felt within 10 days. An alternative interval of five days was tried and gave essentially similar results. A still shorter interval might have been desirable but, because of the small sample size, would have resulted in a great many zero-episode intervals.

When statistical data consist of small integers, i. e., whole numbers, such as number of episodes in a 10-day period, their frequency distribution will be extremely skewed, and a transformation of the variable x(= number of episodes) into $(x+\frac{1}{2})^{1/2}$ is standard practice for stabilizing the variance and eliminating the troublesome problem of frequent periods with zero episodes (Bartlett [9]). We accordingly transformed the multiple sclerosis variable, taking as our multiple sclerosis episode rate

$$y=\frac{(x+\frac{1}{2})^{1/2}}{N}$$

where x = number of episodes observed in the period and N = number of patients at risk during the period.

The next step was to calculate, for successive 10-day periods, the product-moment correlation coefficients of various weather factors with this multiple sclerosis rate, singly and in combination.‖

First, we examined the strength of individual weather factors, such as humidity, in determining multiple sclerosis episodes. Finding several factors which individually showed some, though very low, correlation, we examined further to see whether various combinations of these variables operating together would show stronger determination of multiple sclerosis. Some such combinations were found, and so partial correlations were explored in the expectation that most of these weather factors are correlated among one another. If we find a particular factor apparently determining multiple sclerosis episodes, we wish to inquire whether its action is direct or through some third factor.

In presenting the calculations, we give the value of D, the coefficient of determination, as well as the more familiar r, the correlation coefficient. D is equal to r^2 and is preferred over r because it expresses exactly the degree of determination of the dependent variable (multiple sclerosis) by the independent variable (or variables). Thus, an r of 0.22 for correlation of multiple sclerosis with temperature change reduces to a D of 0.05, indicating that 5% of the variation in multiple sclerosis episodes can be accounted for by variation in temperature change, and 95% by other factors. This gives a clearer picture of the relative importance of temperature changes as a possible cause than does the r coefficient alone. It must be emphasized that statistical analysis of this sort measures only the varying together (covariance) of two or more variables, and does not of itself imply causal relationship. A significant correlation or determination coefficient is a necessary, but not sufficient, condition for the imputation of a cause-effect relationship.

‖ References 10 and 11.

TABLE 2.—*Simple Correlations: Determination of Multiple Sclerosis Episodes by Weather Factors Taken Singly*

Weather Factor	How Measured	Period, Days	No. of Periods	r	D
1. Temperature level	Mean of 10 daily means	10	135	− 0.036	0.0016
2. Temperature diurnal range	Mean of 10 daily maximum-minimum ranges	10	144	+ 0.16 *	0.026 *
3. Temperature diurnal range	Same, with exclusion from risk of patients who have had an episode in previous 90 days (refractory period)	10	135	+ 0.141	0.020
4. Temperature day-to-day changes in maximum: absolute differences	Mean of 5 absolute differences between successive daily maximum temperatures	5	276	+ 0.051	0.003
5. Temperature day-to-day changes in maximum: directional	Mean of 5 signed differences between successive daily maximum temperatures	5	274	+ 0.06	0.004
6. Humidity, relative	Mean of 10 daily mean relative humidity readings	10	144	− 0.065	0.004
7. Sunshine	Mean of 10 daily percentages of possible sunshine	10	144	− 0.001	0.000
8. Solar-radiation winter levels	Mean of 10 daily readings, Oct. through April	10	70	+ 0.086	0.007
9. Solar-radiation summer levels	Mean of 10 daily readings, May through September	10	58	− 0.057	0.003
10. Solar-radiation day-to-day change: absolute	Mean of 10 absolute differences between successive daily totals of solar radiation	10	125	+ 0.06	0.004
11. Solar-radiation day-to-day decreases	Mean of day-to-day decreases in period	10	125	+ 0.07	0.005
12. Solar-radiation day-to-day increases	Mean of day-to-day increases in period	10	125	+ 0.04	0.002
13. Wind velocity	Mean velocity for period	10	135	− 0.026	0.007
14. River run-off, Ottawa River	Mean day-to-day change, absolute	10	141	+ 0.08	0.001

* Indicates the coefficient is significantly different from zero at 5% level, i. e., that sampling from a population with zero correlation would produce this high a correlation less than 5% of the time. Critical value of r is 0.15.

All simple, partial, and multiple correlations, and the intercorrelations, of all the variables were computed. Table 1, for brevity, presents only the principal correlations involved in the hypothesis of weather influences on multiple sclerosis.

FINDINGS

The zero-order correlations of multiple sclerosis episode rate (suitably transformed) with weather factors described are presented in Tables 2 to 4.

TABLE 3.—*Multiple Correlations: Determination of Multiple Sclerosis Episodes by Weather Factors in Combination*

	Weather Factors		No. of Periods	r*	D
15.	Temperature range and temperature level	(2) (1)	135	+ 0.22	0.05
16.	Temperature range and humidity	(2) (6)	135	+ 0.19	0.04
17.	Temperature range and sunshine	(2) (7)	135	+ 0.20	0.04
18.	Temperature range and wind	(2) (13)	135	+ 0.17	0.03
19.	Temperature range, humidity, and sunshine	(2) (6) (7)	135	+ 0.21	0.04
20.	Temperature range, temperature level, and wind	(2) (1) (13)	135	+ 0.23	0.05

* Critical value of r is 0.48. Hence none of the multiple correlations is "significant."

TABLE 4.—*Partial Correlations: Determination of Multiple Sclerosis Episodes by Single Weather Factors, Others Being Held Constant*

	Predictor Factor		Factors Held Constant	r*	D
21.	Temperature range	(2)	Wind (13)	+ 0.17†	0.03†
			Temperature level (1)	+ 0.21†	0.04†
			Temperature level (1) and wind (13)	+ 0.23†	0.05†
			Humidity (6)	+ 0.09	0.01
			Sunshine (7)	+ 0.15†	0.02†
			Sunshine (7) and humidity (6)	+ 0.21†	0.04†
22.	Temperature level	(1)	Temperature range (2)	— 0.13	0.02
			Wind (13)	— 0.06	0.00
			Wind (13) and temperature range (2)	— 0.15†	0.02†

* Critical value of r is 0.15. Significant correlations are marked with dagger.

COMMENT AND CONCLUSIONS

Local climate factors have been investigated for possible correlation with frequency of multiple sclerosis episodes in a group of patients of the chronic remitting type, with the following findings:

1. No significant monthly or seasonal variation in rate of episodes is evident.

2. The diurnal temperature range shows a low but significant positive correlation with multiple sclerosis episodes. This factor alone accounts for about 3% of the variation in multiple sclerosis episodes.

3. Several other weather factors—temperature level, relative humidity, sunshine, solar radiation, wind velocity, and river run-off, which integrates all the weather factors—show no appreciable correlation with multiple sclerosis episodes, but, because of some correlation with temperature changes, obscure the temperature relationship. When these other factors are held constant (partial correlation), the determination of diurnal temperature range on multiple sclerosis rises to about 5%.

4. The temperature changes that have greatest effect are the maximum-minimum range in a 24-hour period (2, Table 2). Temperature changes as between one day's mean or maximum and the next day's have very little effect (4, Table 2). Nor does it matter whether the day-to-day changes in temperature are upward or downward (5, Table 2). This indifference to the direction of change was observed also in solar radiation (10, 11, and 12, Table 2). Thus, our analysis would tend to support the frequent observation that patients with multiple sclerosis suffer increased disability in periods of rapidly changing weather, which may be either unusually warm or unusually cold.

5. About 95% of the variations in multiple sclerosis episodes are attributable to factors other than the macroclimate factors reviewed in this study. Since sudden outdoor temperature shifts (within a 24-hour period) show a significant effect, it might be expected that at least some of the unexplained 95% of variations is due to factors affecting the microclimate of the individual patient, i. e., his clothing, activity, housing, etc. The findings suggest that further study might reveal some small advantage to be obtained by having a patient adopt clothing, housing, and activity habits designed to stabilize his

heat loss and to prevent sudden changes in this respect.¶

¶ Kurland and associates,[12] in a recent review of the etiologic significance of recent epidemiologic and genetic studies, concluded that there was no reliable information linking either onsets or exacerbations with seasonal variations or weather factors. Whether the slight weather effect on the course of the disease found in our study has any implications pertinent to etiology is still to be determined.

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News and Comment

GENERAL NEWS

Congress of the Society of German Neurologists and Psychiatrists.—The Congress will be held in Hamburg, Sept. 19-22, 1955. The main subjects are Motility and Motor Behavior and The Training of the Neurologist. For information, address Dr. Magun, Nervenklinik, Hamburg-Eppendorf.

Centenary of Luis Barraquer Roviralta.—The centenary of Luis Barraquer Roviralta, the founder of Spanish clinical neurology, will be celebrated in Barcelona, Spain, on Oct. 15, 1955. Interested physicians may communicate with the secretary, L. Barraquer-Bordas, Lauria, 102, Barcelona, preferably before Sept. 1.

The Midwest Regional Research Conference of the American Psychiatric Association.—The Conference is being held in Galesburg, Ill., on Sept. 16-17, 1955, under the cosponsorship of the University of Illinois and the Galesburg State Research Hospital. The theme of this meeting will be the newer psychopharmacology.

A New Treatment of Status Epilepticus

Intravenous Injections of a Local Anesthetic (Lidocaine)

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Status epilepticus is a serious complication which sometimes occurs in epileptics even when the disease seems to be under control with the aid of antiepileptic drugs. The status often occurs in connection with acute brain injuries and also during the early postoperative course of brain operations. In Europe status epilepticus is usually treated with intravenous barbiturates (Somnifene; Hypnofen [20% solution of diethylbarbituric and allylisopropylbarbituric acid]), which generally stop the fit provided that the patient is deeply anesthetized. This treatment, however, has certain disadavantages. The deep sleep often results in unsatisfactory ventilation of the lungs, which may give rise to respiratory complications. Furthermore, it is impossible to foresee the duration of the status in progress, and therefore the patient may be anesthetized for an unnecessarily long time, since the barbiturates are slowly eliminated. When the status develops during the days immediately following a brain operation, this therapy has still another disadvantage in that the symptoms of a developing postoperative clot may be masked. In an investigation of experimental epilepsy on cats and monkeys, Bernhard and Bohm * showed that intravenous injections of local anesthetics, depending on the dose, diminish or abolish the epileptic attack evoked by electrical cortical stimulation. Judged on the basis of toxicity and effectiveness against experimental epilepsy, lidocaine proved to be a more suitable anticonvulsant than any of the other substances tested [3] (procaine, butethamine [Monocaine], Intracaine ([β-diethylaminoethyl-*p*-ethoxybenzoate hydrochloride], tetracaine).

In the present work a detailed description is given of the anticonvulsive effect of intravenously administered lidocaine on prolonged epileptic attacks in 10 human cases.† In the cases of status epilepticus, a 1% or 2% solution of lidocaine (without epinephrine) was used in intravenous saline or dextrose drip.

REPORT OF CASES

CASE 1.—The patient was a 20-year-old girl who had suffered from daily grand mal and petit mal attacks since 4 years of age. Various antiepileptic drugs had no effect. An x-ray of the skull showed normal conditions. The EEG showed bilateral synchronous activity from most parts of the hemispheres. Encephalography proved that the left lateral ventricle was slightly dilated.

The grand mal attacks always started in the following way: The patient cried out, sat up in her bed, and turned to the right. Then the clonic spasms started gradually and were more pronounced on the right side. The cramps then gradually decreased, and after they had finished, she started to chew and spit and put out her tongue. The duration of the attacks varied between two and four minutes. The patient was unconscious during the attacks but woke up a few minutes after their termination.

On three occasions 0.6 to 1.2 mg. of lidocaine per kilogram of body weight was given in a single dose

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Lidocaine was synthesized by Löfgren (References 7 and 8). Xylocaine is the trade name of the Astra Pharmaceutical Company; the nonproprietary names are lidocaine and lignocaine.

* References 1, 2, and 3.

† A brief note on our first five cases was made in preliminary communications (References 1 and 2).

intravenously as soon as the clonic spasms had started. On all these occasions the cramps suddenly stopped 20-30 seconds after the injection, and there was no sign of chewing and salivation.

Comment.—The fact that lidocaine stopped the epileptic attack and abolished the postictal phenomena at three different times proves that it has an anticonvulsive effect.

CASE 2.—The patient was a 29-year-old man who had suffered from epileptic attacks of grand mal type since 2 years of age. The attacks began with loss of consciousness; soon afterward the spasms started and increased in frequency and then decreased gradually. The duration of the attacks varied from 15 to 30 minutes. After the attacks the patient slept for some hours.

On two occasions lidocaine was injected intravenously in a single dose during an attack.

On the first occasion, the attack had been going on for 14 minutes and the frequency of the spasms indicated that the attack had not passed its maximum. Injection of 1.5 mg. of lidocaine per kilogram of body weight was given intravenously. The cramps diminished 20 seconds after the start of the injection and stopped completely in another 40 seconds, at which time the injection was completed. The spasms ceased abruptly, and the patient slept for three hours. He then had a second severe attack, with generalized spasms. When this fit had lasted for 11 minutes, without any tendency to stop, 2 mg. of lidocaine per kilogram was injected intravenously. At this time, also, the spasms ceased within one minute, and afterward the patient slept for some hours.

Comment.—Two sustained epileptic attacks of grand mal type, which had not passed maximum, were cut short with an intravenous injection of lidocaine. As in Case 1, a diminution of the spasms began 20-30 seconds after the injection had started. The observations on this case thus prove that lidocaine has a pronounced anticonvulsive effect on epileptic fits in humans.

CASE 3.—The patient was a 68-year-old woman who had an arachnoidal cyst in the left parietal region, which was emptied in 1943. After the operation she had no symptoms until June, 1953, when a right-sided Jacksonian attack appeared and was followed by postictal right-sided hemiparesis, which disappeared after one week. Since the end of 1954, however, increasing weakness of the right arm and leg had developed. In May, 1954, the cyst was again emptied. Three days after the operation the patient had a right-sided Jacksonian attack without loss of consciousness. The spasms were most pronounced in the arm. At the beginning of the attack the patient got 2 ml. of Hypnofen (1 ml. intravenously and 1 ml. intramuscularly), without any effect.

When the attack had lasted for three hours, 1 mg. of lidocaine per kilogram of body weight was injected intravenously. Thirty seconds after start of the injection the spasms ceased in her extremities. The cramps in the shoulder and trunk diminished, stopped completely after 10-15 minutes, and did not return.

Comment.—In this case, also, there was a striking antiepileptic effect of lidocaine 30 seconds after the injection had started. The patient was conscious during the whole time; the injection did not cause any discomfort and did not make her feel drowsy.

CASE 4.—The patient was a 31-year-old woman who had suffered since 1937 from frequent epileptic attacks of both grand mal and petit mal type. The encephalogram was normal. The EEG showed a focus in the left temporal region. Operation was performed in April, 1954. The electrocorticogram showed pathological activity, localized to the anterior part of the temporal lobe, which was resected. Histological examination showed that the removed brain tissues were normal. The day after the operation the patient had some generalized epileptic attacks. These fits continued during the next eight days, with varying frequency. Besides these attacks she also had fits which consisted of the head and eye turning to the right and of spasms in the right arm and the right side of the face. On the fourth postoperative day she became aphasic, and after still another day the right arm became paretic. Reoperation on the eighth postoperative day disclosed nothing which could explain her status epilepticus. In spite of large doses of Hypnofen and antiepileptics, the epileptic fits continued. She became restless, and her condition deteriorated rapidly.

On the 20th day after the first operation she received an intravenous drip of 1 mg. of lidocaine per kilogram of body weight per hour. The generalized fits disappeared, and the right-sided spasms diminished in frequency and duration. During the lidocaine treatment she became quiet, and after 12 hours she could say some words. The intravenous injection was then stopped. During the two following days her condition improved rapidly. The attacks gradually diminished in frequency and duration and stopped after one more day.

Comment.—In this case generalized epileptic attacks could be eliminated with an intravenous drip of 1 mg. of lidocaine per kilogram of body weight per hour. The right-sided spasms were also influenced, the frequency and the duration of these fits

being diminished. Since her status epilepticus was not influenced by the common antiepileptic treatment during a three-week period, our conclusion is that the improvement which occurred in connection with the lidocaine drip is to be attributed to this treatment.

CASE 5.—The patient was a 31-year-old man who had suffered from diabetes mellitus since 12 years of age. Because of a progressive disturbance of vision since the end of 1952, the patient was submitted for hypophysectomy in July, 1954. The postoperative course was uneventful during the first nine days. At that time the patient began to have absences, with deviation of the eyes to the left. The frequency of these attacks increased progressively, and after still another day these attacks occurred once an hour with a duration of one to five minutes.

When at that time some generalized fits also appeared, 2 mg. of lidocaine per kilogram of body weight per hour was administered in an intravenous drip. The attacks then stopped completely. When the drip had been running for two hours, the rate of administration was diminished by mistake and soon thereafter some absences appeared, but they vanished as soon as the dose of lidocaine was raised. The patient was free from attacks for 12 hours. At that time the treatment was stopped and the absences appeared again, but the patient had no spasms. The treatment was therefore continued, and after another eight hours the absences disappeared. Four hours later the lidocaine drip was stopped, and the absences appeared again and increased gradually in frequency and duration. Twenty-four hours after the treatment the frequency and duration of the attacks were the same as before the lidocaine treatment. Some days later an intravenous drip of lidocaine (2 mg. per kilogram per hour) was introduced. The absences, with turning of the head to the left, were at that time very frequent and had appeared every fifth to sixth minute for several hours. The treatment continued for four hours, and during this time there were only two absences, without turning of the head. Forty minutes after that the treatment was stopped, and the patient had an attack with spasm in the left arm and leg.

Comment.—This case illustrates one of the advantages of treating sustained status epilepticus with lidocaine. Since lidocaine is rapidly eliminated, it is possible with this treatment to determine whether the status still is going on by interrupting the administration of lidocaine, thus avoiding unnecessarily prolonged treatment.

CASE 6.—The patient was a 42-year-old woman who had suffered from right-sided Jacksonian fits for one year. Arteriography and encephalography demonstrated a meningioma in the left parietal region. The tumor was removed in October, 1954. During the first postoperative day she had frequent attacks of right-sided spasms in the face and arm. Injection of 2.5 ml. of Hypnofen intramuscularly had no effect on the spasms. Progressively increasing drowsiness developed, and on the next day she was reoperated on and an extradural hematoma was removed. The spasms continued as before, and since she was still unconscious the following day, she was again operated on. There was no clot. The spasms continued with a frequency of four attacks per hour and a duration of two to five minutes.

The patient then got an intravenous drip with a dose of 2 mg. of lidocaine per kilogram of body weight per hour. When the drip had been running for 10 minutes, there was an attack of spasms, which lasted for two minutes. Not until six hours later was there a new attack, of slight spasms, in her face. Her condition improved gradually, and when the drip was stopped, after eight hours, she had regained consciousness. Twenty-four hours later there was only a slight attack of spasms in her face.

Comment.—Judging from the result of the treatment in this case, it is probable that the blood concentration of lidocaine was very low when the attack of spasms occurred, 10 minutes after the intravenous drip had started.

CASE 7.—The patient was a 20-year-old woman with symptoms of increased intracranial pressure for half a year. Encephalography demonstrated a left-sided central expansive lesion, obliterating the posterior part of the third ventricle. A right lateral ventriculocisternostomy was performed (Torkildsen procedure) in September, 1954. The postoperative course was uneventful for three weeks. At that time she suddenly had left-sided tonic-clonic spasms, with increasing frequency. Injection of 0.1 gm. of phenobarbital (Phenemal) intramuscularly had no effect on the attacks. Two hours after the beginning of the status epilepticus the intervals between the attacks were one to one and a half minutes, and the attacks lasted for 30 to 40 seconds.

Lidocaine, 3 mg. per kilogram of body weight, was then injected intravenously. After the injection six attacks, at increasing intervals, occurred during the next 17 minutes, after which no more attacks occurred.

Comment.—In the two last cases (6 and 7) the spasms did not stop instantly after the intravenous injection of lidocaine. The frequency of the attacks, however, diminished

immediately after the injection had started, and the spasms finally disappeared.

CASE 8.—A 39-year-old man was admitted to the hospital in October, 1954, after a severe head injury. After two days, short attacks of spasms on the left side of the body occurred, increasing in frequency and strength, and turning into very severe generalized seizures during the next day. The interval between the attacks was 10 minutes and the duration one-half to one minute.

The patient received 2 mg. of lidocaine per kilogram of body weight per hour as an intravenous drip. The generalized attacks, however, broke through as before, and therefore the patient got 2 mg. of lidocaine per kilogram of body weight intravenously in a single dose. The effect of this supplementary injection was striking. The spasms were reduced to slight jerks in the left arm. However, 20 minutes later he had a generalized seizure, which was not as severe as before and which lasted only 10 seconds. The jerks in the left hand then increased progressively and involved the arm. Twenty minutes later a generalized seizure developed. He then got another single dose of 2 mg. of lidocaine per kilogram, after which injection the spasms in the left hand and arm diminished. One hour after the injection a generalized seizure broke through, followed by two attacks during the course of 10 minutes. Four milligrams of lidocaine per kilogram was then injected in a single dose. Again, the spasms in the left arm diminished, but 20 minutes after the last injection a generalized seizure occurred, which, however, was not as severe as the earlier ones. During the whole time the intravenous drip had been running at a rate of 2 mg. of lidocaine per kilogram of body weight per hour. After this treatment the patient had some generalized seizures and attacks of left-sided spasms, with an interval of three to six minutes and a duration of one-half to one minute.

Since the attacks could not be stopped with the continuously running intravenous lidocaine drip and the supplementary injections described, 2 ml. of Hypnofen and 4 mg. of lidocaine per kilogram were injected intravenously. The effect of this injection was striking. The patient became quiet, and there were only slight spasms in the left hand, which occurred at intervals of 10 minutes during the next two hours. After that time the arm was also involved. In addition to the lidocaine administered through the intravenous drip, the patient got 2 mg. of lidocaine and 0.5 ml. of Hypnofen intravenously in single doses every hour for four hours. During this time no generalized fits occurred, but only slight spasms in the left arm.

At this time the lidacaine treatment was stopped, after having run for 18 hours. The generalized fits did not occur any more. During the next two days there were only frequent attacks of slight spasms in the left hand, which gradually stopped and did not return.

Comment.—There seems to be no doubt of the anticonvulsive effect of lidocaine on the very severe status epilepticus in this case. Continuous administration of 2 mg. of lidocaine per kilogram of body weight per hour was, however, not sufficient to stop the generalized seizures. For this purpose a single dose of 2 to 4 mg. of lidocaine per kilogram per hour was required. The fits then were abolished for a period which corresponded to the time during which we have found it impossible to provoke an epileptic attack in animal experiments by electrical stimulation of the cortex after a corresponding intravenous dose of lidocaine.[3]

In addition, this case shows the good effect of a combination of a small dose of barbiturate and a local anesthetic, which we already have demonstrated in the experiment on animals.[3] If only Hypnofen had been used as an anticonvulsant, it would have been necessary to anesthetize this patient deeply during at least 18 hours, with great risks of lung complications.

CASE 9.—The patient was a 27-year-old woman who had suffered from diabetes mellitus since 5 years of age. For two years she had been blind in one eye and had progressive impairment of vision in the other. The patient was admitted for hypophysectomy in October, 1954. The postoperative course was uneventful during the first two weeks. At that time short absences occurred, and the next day right-sided spasms in the face and arm developed. During the two following days generalized seizures occurred with increasing frequency. The intervals between the attacks were 5 to 10 minutes, and the duration of the attacks was about one minute.

An intravenous drip of 2 mg. of lidocaine per kilogram of body weight per hour was given. Since the patient was very restless, it was necessary to inject 1 ml. of Hypnofen intravenously before the beginning of administration of the drip. This injection had no effect on the fits, but the patient became quieter. When the lidocaine drip had been running for half an hour, the frequency and duration of the attacks diminished. After two hours the dose of lidocaine was increased to 4 mg. per kilogram per hour and the frequency of the attacks diminished further. When, after two hours, the dose was raised to 6 mg. per kilogram, the attacks disappeared for two hours, but appeared again. Injection

of 1 ml. of Hypnofen and 2 mg. of lidocaine per kilogram was then made intravenously in a single dose. The generalized fits disappeared completely, and there were only slight right-sided spasms in the face and arm. After one hour the lidocaine treatment was stopped.

After another 12 hours the frequency and duration of the right-sided spasms increased. When one generalized seizure occurred, a lidocaine drip with 2 mg. per kilogram per hour was again instituted. During the next two hours these attacks appeared five times. She then got 2 mg. of lidocaine per kilogram intravenously in a single dose, and at the same time the lidocaine dose in the drip was raised to 6 mg. per kilogram per hour. The attacks then disappeared completely, and the treatment was stopped after another four hours.

During the following 12 hours she had no seizures, but after that they appeared again. During two hours she had eight grand mal attacks, although she received 2 mg. of lidocaine per kilogram per hour in an intravenous drip. After a single intravenous dose of 4 mg. of lidocaine per kilogram, the attacks disappeared for three hours. Since after that time eight grand mal seizures appeared during one hour, the lidocaine dose in the drip was raised to 3 mg. per kilogram per hour and a supplementary dose of 4 mg. of lidocaine per kilogram was injected intravenously. The attacks disappeared for three hours, and she then had four generalized seizures during half an hour. It was found that the drip did not work satisfactorily, and when the patient again received 3 mg. of lidocaine per kilogram per hour, the attacks disappeared. The treatment was continued for 12 hours more, and the patient had no further attacks.

Comment.—In this case, also, a dose of 2 mg. of lidocaine per kilogram per hour seemed to be too low to cut short the status epilepticus. Even a dose of 4 mg. of lidocaine per kilogram per hour did not prevent the attacks from breaking through. However, a combination of this dose of lidocaine and a small dose of barbiturate abolished the attacks. The anticonvulsive effect of the combined treatment cannot be attributed to the injection of Hypnofen alone, since, when her status epilepticus began, the same dose (1 ml.) was given intravenously without any effect on the fits.

CASE 10.—The patient was a 3-year-old girl who had suffered from right-sided Jacksonian fits for one year. During the last months the attacks had increased in frequency and occurred daily. Right-sided hemiparesis had slowly developed. Air encephalography showed dilated ventricles and the EEG a diffuse abnormal activity.

After air encephalography the fits increased in frequency and turned into status epilepticus. Lidocaine, 4 mg. per kilogram per hour, was injected intravenously in a single dose, and after 30 seconds the spasms diminished; they disappeared completely after 5 minutes. The spasms, however, reappeared 15 minutes after the injection, and they slowly increased in strength and frequency. After three hours her condition was the same as before the treatment. Intravenous Hypnofen, 0.25 ml., was given, with no effect on the spasm. An intravenous drip with 4 mg. of lidocaine per kilogram per hour was then introduced. The spasms diminished in frequency and strength but occurred every sixth minute during the following hour. At that time a supplementary single dose of 4 mg. of lidocaine per kilogram was injected intravenously. After this injection the spasms appeared only in the face, and the attacks occurred at intervals of 30 minutes. Three hours later the attacks began to increase in frequency, and the spasms involved also the arm and leg. An injection of a supplementary dose of 4 mg. of lidocaine per kilogram and 0.25 ml. of Hypnofen abolished the spasms almost completely for three hours, at which time a new supplementary dose was injected, with the same good result. During the following 10 hours the patient got only 4 mg. of lidocaine per kilogram per hour, administered by the intravenous drip. During this time the attacks slowly increased in frequency (every three minutes) and strength and finally involved the leg and arm. Hypnofen, 0.5 ml., was then injected intravenously, but it had no effect on the spasms. The rate of the lidocaine drip, which had been running during the whole time, was then raised to 6 mg. per kilogram per hour, and a supplementary dose of 6 mg. of lidocaine per kilogram was injected. The effect on the spasms was striking, and during the following seven hours there were only short-lasting spasms in the face, occurring with an interval of 30 minutes. The treatment was then stopped, and during the following 12 hours the attacks gradually decreased in frequency and strength; after that time her condition was the same as before the status began.

Comment.—In this case intravenous injections of high doses of barbiturates had no effect on the spasms. It would have been necessary to anesthetize the patient deeply in order to cut short this sustained status with the aid of barbiturates. However, with a combination of lidocaine and Hypnofen the barbiturate dose could be kept very low, thus diminishing the risks of lung complications.

GENERAL COMMENT

In earlier experiments by Bernhard and Bohm it was shown that epileptic attacks evoked by electrical cortical stimulation in cats and monkeys could be abolished by intravenous injections of local anesthetics.‡ Since lidocaine appeared to be the most favorable anticonvulsant for clinical use among the different local anesthetics tested, and since there is considerable evidence that the intravenous injection of lidocaine in humans carries little risk of complications,[5] it was used in the present clinical investigation. The results show that lidocaine is effective against epileptic fits in humans. The animal experiments, mentioned above, showed that the effect of an intravenous injection of lidocaine is temporary (20-60 minutes, depending on the dose), as was to be expected from what is known about the elimination of the drug (Wiedling,[9] 1952). In order to prove that intravenous lidocaine has an anticonvulsive effect on epileptic fits in humans, it was therefore necessary to show that an intravenous injection of the drug stops or modifies an epileptic attack which is going on, the characteristics of which are known from previous observations. Cases 1 and 2 were chosen for this purpose, and they show that a single intravenous dose of 1 to 2 mg. of lidocaine per kilogram of body weight may stop an epileptic attack after a delay which allows for the circulation time (20-30 seconds). As expected from the animal experiments, the protective effect of a single intravenous dose is temporary.§ In six cases lidocaine was given in intravenous drip in order to prevent epileptic attacks for a longer period. Depending on the severity of the status epilepticus, the lidocaine dose had to be varied from case to case. Some cases (5 and 6) reacted favorably to 2 mg. of lidocaine per kilogram per hour. In other cases, however, this dose was not sufficient to stop the fit but diminished the frequency and duration of the attacks. In some cases with very severe status epilepticus (8, 9, and 10) single intravenous doses were given as a supplement to the intravenous drip. When the blood concentration of lidocaine was raised in that way, even very severe attacks could be cut short, e. g., Case 9. In the course of the clinical investigation we found that a small dose of a barbiturate (Hypnofen) increased the effectiveness of lidocaine in a very striking way. The synergic action of a barbiturate and lidocaine was therefore studied in the animal experiments,[3] and they showed that a barbiturate in doses too small to affect the experimental epileptic fit increased the antiepileptic effect of lidocaine in a very striking way. A similar study on human epileptics with the use of photic activation gave similar results,[4] The synergic anticonvulsive action of a barbiturate and lidocaine was studied in Cases 8, 9, and 10. They show that Hypnofen, in doses too small to influence the epileptic attack, markedly increased the anticonvulsive effect of lidocaine. Probably this combination therapy is to be preferred and is necessary in when very large doses of lidocaine are to be avoided. The dose of the barbiturate can be kept so low that the complications of its sedative effect are avoided. On the other hand, when such a small dose of a barbiturate is added, the lidocaine dose can be kept so low that there is no risk of toxic reactions.

Actually, intravenously administered lidocaine seems to carry little risk of toxic reaction. Clive-Lowe, Gray, and North,[5] who used lidocaine together with succinyldicholine and nitrous oxide for a combination narcosis for surgical operations, state that 750 mg. of lidocaine can be given intravenously without risks for one hour. If the narcosis has to

‡ References 1, 2, and 3.

§ A study on one case of epilepsy was published by Halldin[6] (1954), in which he reported that an injection of 2 ml. of a 2% lidocaine solution (less than 1 mg. per kilogram of body weight) into the submucous tissue once a week diminished the frequency of the epileptic attacks from one attack every 12th day to one attack every 40th day. During the whole period the patient also was treated with different anticonvulsants (barbiturate and hydantoid preparations). Our animal experiments (References 1, 2, and 3), as well as the present clinical investigations, show that the change in the frequency of the attacks probably cannot be ascribed to the lidocaine injections.

be prolonged further, the lidocaine dose ought to be reduced to 450 mg. per hour, according to these authors. In pharmacological and anesthesiological literature, it is emphasized that local anesthetics in large doses can produce spasms. In the large material mentioned above (1000 cases), large doses of lidocaine were injected, and there were only 3 cases in which spasms occurred. In these cases the dose was extremely high and the rate of injection very rapid. When the injection was slowed down, the spasms ceased.

In our investigation made on patients with an increased tendency to convulsions, no such exciting effects have been noticed, even when a single supplementary dose of up to 6 mg. per kilogram was added to a continuously running intravenous drip of 6 mg. per kilogram per hour (Case 10).

SUMMARY

A description is given of the anticonvulsive effect of an intravenously administered local anesthetic (lidocaine) on prolonged epileptic attacks in 10 human cases. Lidocaine in intravenous drip was found to be of great use in the treatment of status epilepticus. It was also found that a barbiturate in doses too small to influence the epileptic attack increases the anticonvulsive effect of lidocaine. Since the supplementary dose of the barbiturate can be kept so low that the complications of its sedative effects are avoided, this combination therapy is to be recommended in the treatment of severe status epilepticus. Therefore this treatment is especially useful against epileptic fits occurring during the early postoperative course in cases of brain operations.

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Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Walter Wegner, M.D., President, Presiding
Regular Meeting, Jan. 20, 1955

Experimental Studies of Brain Injury. Dr. John S. Meyer, with the assistance of HM3 Ernest Martel.

Experimental concussion, contusion, brain laceration, and ischemia were studied in terms of local cortical oxygen availability (EPG), blood flow, pH, jugular venous pressure, intracranial pressure, blood pressure, respiration, EEG, and steady potentials (SP [D.C.]).

Systemic arterial oxygen saturation was measured photoelectrically. Cortical oxygen availability was recorded with the polarograph described by Meyer, Fang, and Denny-Brown. Microglass thermistor electrodes indicated cortical blood flow. SP potentials were measured with a D.C. millivoltmeter and D.C. amplifier.

Temporary cerebral ischemia causes similar changes of cortical EPG and temperature, with local acidity and resulting vasodilatation. Respiratory anoxia produces parallel changes in arterial oxygen saturation and cortical EPG. The EPG falls to low levels first; after two minutes the EEG becomes equipotential, with rapid SP negativity (7 mv.) of the cortex with respect to the white matter.

Concussion causes immediate reversible cortical SP negativity (7 mv.), indicating transient neuronal paralysis and an increase in cortical EPG, due to neuronal paralysis and increased blood flow.

Contusion produces negative SP shifts, arising from the damaged area of longer duration, complicated by local hypoxia and ischemia with further brain damage. Laceration results in widespread local hypoxia and ischemia, due to bleeding and vascular spasm.

The initial effect of brain trauma is neuronal paralysis, later complicated by ischemia and anoxia. In concussion neuronal paralysis is the only effect.

DISCUSSION

Dr. Walter Wegner: As indicated in the paper, the attempts to elucidate the mechanism of concussion have been many. Some bizarre proposals have been made to explain how the brain is injured. There is still much to be done. It is satisfying to find a piece of work of this sort, which is well documented and convincingly presented, to explain some of the mechanisms of concussion. The methods used have been ingenious.

Dr. Robert S. Schwab: This method gives us many variables that would be difficult to get in human material. Have thresholds for evoked response been studied during concussion?

Dr. Peritz Scheinberg: If this method of measuring cerebral metabolism is technically satisfactory, it may offer more than other methods in giving information about cerebral tissues. In Dr. Meyer's paper several things were of interest: Some findings represented an apparent contradiction to what we had learned with other procedures. Oxygen breathing in these animals resulted in considerable increase in oxygen availability in the tissues as measured by the EPG. This change in oxygen availability was in direct proportion to alterations in blood presssure, a finding which seems to be in contrast to what we understand about reactivity of cerebral vessels. Ordinarily cerebral vessels respond to changes in blood pressure by regulating the blood flow locally. This apparent contradiction made me wonder whether in these animals the anesthetic agent itself might not have resulted in some alteration in the physiological reactivity of the vessels, making it difficult to know what would happen under normal circumstances.

Dr. John S. Meyer: I believe, Dr. Schwab, that Groat, Magoun, Dey, and Windle showed that in either acceleration or compression concussion the cortical threshold of excitation (supranuclear pathways) was temporarily raised.

We have found that three or more minutes after an occipital lobe contusion the evoked response in the electrocorticogram can still be elicited.

I think we have many of the answers to the questions Dr. Scheinberg raised. I do not believe our findings contradict what has been learned from other procedures if it is recalled what we have been measuring. We measure the oxygen availability of tissues which may have differences from measurements of the cerebral blood oxygen composition. Oxygen breathing produces a more pronounced rise in the cerebral tissue space than in the arterial oxygen saturation. There is normally a close balance between neuronal consumption of oxygen and oxygen brought to the tissue by the vessels. When the blood oxygen is raised by breathing oxygen after air, there is a large rise in the oxygen availability of the tissue space. This is a very consistent finding, and a similar rise in oxygen tension has been shown by others to occur in the myocardium and skin with oxygen breathing. We now have a considerable mass of data showing that blood vessels may locally regulate their flow. Anesthesia appears to be an important factor in relation to minor compensatory mechanisms in the cerebral circulation following alterations in systemic blood pressure, but our findings of a critical level of blood pressure of about 50-60 mm. of mercury below which cerebral blood flow begins to fail has recently been confirmed in unanesthetized man by Moyer and others, using the nitrous oxide method.

The changes in cortical EPG and temperature immediately after concussion are compatible with decreased neuronal consumption of oxygen (i. e., paralysis); later changes are due to increased cerebral blood flow. The same sequence occurs when the animal is concussed during artificial respiration.

The EPG measures cerebral tissue oxygen availability in small areas; this measurement may be influenced by (1) changes in blood pressure and local blood flow, (2) oxygen saturation of blood, and (3) neuronal consumption of oxygen. It, therefore, measures only local blood flow if the other parameters are constant.

Tussive Syncope. Dr. Simon Horenstein.

Tussive syncope results from critical fall in cerebral blood flow due to a combination of factors, each of which in itself is not sufficient to cause an attack of unconsciousness. Of these, reduced cardiac output consequent upon prolonged coughing is the most important. This alone rarely causes syncope, and further reduction in cerebral blood flow resulting from phenomena associated with abdominal ptosis, varicose veins, previous respiratory alkalosis, or emphysema must occur in appropriate time relationship to cause a degree of cerebral anoxia sufficient to produce unconsciousness. The electroencephalographic abnormality characteristically associated with tussive syncope is marked by the development of widespread high-amplitude, slow activity, most prominent in the frontal region, which occurs with the start of the attack. This potential lasts only as long as the symptoms of syncope are present and is independent of any other change which may have been present in the record previously. The usual clinical situation involves sudden rising from a chair or bed during a bout of prolonged coughing. This then is followed by syncope. There is no evidence that this disorder arises from purely cerebral causes, although in some cases there had been minor cerebral trauma. Treatment should be directed toward altering the phenomena which in any instance cause cerebral hypotension.

DISCUSSION

Dr. Robert S. Schwab: How serious is this tussive syncope? I had a patient go into one while I was taking blood pressure. How dangerous is it?

Dr. Simon Horenstein: Baker reviewed the literature in 1936. He recorded 2 instances of fatal tussive syncope out of 200 cases recorded at that time. It was never clear from the clinical reports why these patients died. We have had difficulty getting clear EEG's because the patients cough so much that the record is obscure or they cough so little that nothing happens. The easiest way in which to produce the EEG changes is to have the patient sit on a low footstool, stimulate him to cough by putting a catheter into the throat, and encouraging him to stand at the height of the coughing. The case reported by McCann, in which syncope occurred when the bronchoscope was in the larynx, demonstrated a very sharp increase in pulmonary artery pressure. It was thought upon that basis that a factor in preventing returning blood to the left heart was a pulmonary artery spasm. Clinically, a hard, dry, uninterrupted spell of coughing associated with some other phenomenon, e. g., rising from a chair, is crucial. The element of pulmonary artery spasm is nuclear in such cases. A rise in spinal fluid pressure to levels of 780-800 mm. H_2O is not regarded as a factor here.

DR. JOHN S. MEYER: We have made a few observations in experimental animals and have confirmed the mechanisms postulated by Dr. Horenstein. We have caused the Valsalva maneuver in monkeys, recording cortical arterial and venous temperature, EPG, EEG, and jugular venous pressure, together with intrathoracic pressure, respirations, and blood pressure.

Associated with sustained increase in intrathoracic pressure, we have shown that there is a fall in cerebral blood flow and oxygen availability due to an increased cerebral venous pressure and a fall in blood pressure. The EEG activity is diminished in amplitude in this phase.

Tiresias Syndrome: A Case Presentation. DR. PHILIP SOLOMON.

An extraordinary case is presented in which the sex of the patient was changed and then, later, was changed back again. The patient lived her first 13 years as a girl. At a Southern state school for girls an anomaly of her genitals was discovered. She was sent to a large medical school hospital, where she was operated upon several times, given testosterone, and told that she was now a boy. The patient spent the next 13 years, with indifferent success, as a male. Delinquency sent the patient to the state school for boys, where the patient's large breasts caused a problem. A marriage was annulled after four years. Numerous failures and depression caused the patient to return to the medical school hospital, where, after months of psychotherapy and the administration of diethylstilbestrol, she again resumed the role of a female. For the past five years she has lived a confused life, colored by alcoholism and relations with heterosexuals and homosexuals of both sexes.

The patient was admitted to the Boston City Hospital with pneumonia. Since her recovery she has been receiving psychotherapy in the outpatient psychiatric clinic, and she has responded well.

A number of questions raised by a patient such as this are briefly discussed.

Walter Wegner, M.D., *President, Presiding*
Regular Meeting, Feb. 17, 1955

Psychiatric Treatment and Social Structure. DR. F. C. REDLICH, New Haven, Conn.

This report is based on a study during the last four years by A. B. Hollingshead, of the Department of Sociology, and F. C. Redlich, of the Department of Psychiatry, of Yale University, and their co-workers. Material was presented to demonstrate that differences in treatment from the first moment of contact between psychiatrist and patient are marked in the social classes. Referral, type of treatment, intensity of treatment, and methods of rehabilitation differ and seem to favor the upper classes. Actually, such differences in treatment apply to most psychiatric disorders, with the exception, possibly, of the treatment of manic-depressive patients. They are very striking in schizophrenia and in the psychoneurotic group. These differences in treatment were discussed in some detail, and examples were cited which prove that they not only are due to economic differences but seem to be conditioned in part by differences in communication and different value orientations of psychiatrists and patients. Communication between middle-class psychiatrists and lower-class patients seems to inhibit the therapeutic contact and process. This research at the moment is in a state of flux, and the material is being analyzed to permit definite statements. The study, as it was presented, is an investigation of certain sociological aspects of psychiatric practice, although some of the material will throw important light on problems of psychopathology and psychodynamics.

DISCUSSION

DR. JOSEPH J. FOLEY, Middleboro, Mass.: The decision about which class a patient falls into must be a difficult one. Could Dr. Redlich clarify the criteria by which he decided?

DR. WILLIAM MALAMUD: I was very much interested in Dr. Redlich's statement, particularly since I have followed his work for some time. For the sake of clarity, I think it would be well if Dr. Redlich would describe in more detail the classification that was established by Hollingshead, because any interpretation of the reasons for a difference in distribution of neuroses and psychoses in these five groups would have to take into consideration basic principles which were used in developing the classification. I am quite certain that there are important sociodynamic factors which contribute to this difference in distribution. It is also possible,

however, that other factors come in which may be spurious. A number of workers in this area have found, for instance, that there is a tendency to make the diagnosis of neurosis more frequently in private hospitals than in other institutions. Where there is a question of a doubt, the tendency is to err on the side of a milder diagnosis with a better prognosis in the case of private patients. Another factor that may come in is that of the duration of hospitalization and an accumulation of the more chronic patients in places where less active treatment is being undertaken, and, because of that, an artificial increase in proportion of patients suffering from serious illnesses in institutions where less active treatment is being conducted.

Finally, I would like to refer briefly to a statement that Dr. Redlich made, that in the case of indigent patients, where the treatment is being carried out by younger members of the staff, or even medical students, the results are less beneficial because these relatively inexperienced therapists lack the skill and interest that older physicians possess. I will agree with him in regard to skill, but I doubt whether there is less interest and enthusiasm on the part of the younger people.

DR. HARRY SOLOMON: There are at least a thousand questions that can be asked of Dr. Redlich about these findings, particularly as to his interpretations. I would like to say that this is a magnificent piece of work. It gives us all a chance to ask questions and to debate. It is a method that is clear and obvious, and should have been used long ago. It has taken a certain amount of imagination to do the things that seem so necessary. What is highlighted is that a great portion of our community accumulate in large institutions, where they get what Dr. Redlich calls custodial care. There they may deteriorate. Those who do not go through this oppressive control tend to recover. I don't want to question this at this time; one possible explanation is that the majority of people with acute psychosis have in themselves the capacity to get well. Perhaps the treatment they get is more responsible for their long-term process than the disease.

DR. ALFRED H. STANTON, Washington, D. C.: Is it possible for your study to separate out variables, so that one can tell *within* one ethnic group—Italians or Negro, for instance—that the same relationship holds among social classes? Is this related to the ethnic group as a factor?

Because of the problems of understaffing of our mental hospitals, there has been a tendency to rely upon exploiting the relationship of aide and patient for its possible therapeutic benefit; similarly, the interrelationship among patients has been studied by group psychotherapy or patient government. It would seem from your work that these two approaches might have some unforeseen advantages in overcoming the difficulties which upper- and middle-class doctors might have in communicating with patients. Is that a fair implication?

DR. F. C. REDLICH, New Haven, Conn.: I appreciate this discussion. In answer to Dr. Foley: Our criteria for the census study to determine social class are simple, based on Hollingshead's Index of Social Position: education, occupation, area of residence. Each can be clearly classified, scaled, and indexed. It is different in each community. In our more intensive study we used other criteria—many that are characteristic, such as memberships in clubs, churches, patterns of recreations, etc. There are many variables of interest to the psychiatrist as to how people in various social classes live differently, how their aggressive and sexual and dependent behavior are different. For our criteria these three indices which determine social class were used. The reliability and validity from statistical controls are quite high. I wish that on the psychiatric side we had more criteria that are as clear as the sociologists have. They ask why our thinking is not as clear. The answer is, our problems are more complex.

Reliability of Diagnosis: It would seem that upper- and middle-class patients do get "milder" diagnoses from psychiatrists. I remember an instance earlier in my career in a private sanitarium in Europe. A patient from the high aristocracy had schizophrenia. The professor said: "This patient has a little thinking disturbance." I said, "It is schizophrenia." He said, "But you can't say this." In our study we talked to the psychiatrists, looked over the records, and made our own diagnosis. We tried to correct this as much as we could. We were also aware that neuroses may later turn out to be schizophrenia.

In answer to Dr. Stanton, I think he is right that, on the basis of what we know, group therapy and something borrowed from play therapy may be proper forms of treatment among the lower classes. This might be difficult among members of the middle and upper classes, who could not talk in a group as someone from the lower classes could do.

Hippocampal Studies: Their Possible Bearing on Neuropsychiatry. DR. PAUL D. MACLEAN, Hamden, Conn.

The authors reviewed stimulation and electroencephalographic studies that indicate the role of the hippocampus in regard to awareness, rage, pleasure, pain, and other emotions. Motion pictures were shown to illustrate alteration of conditioned avoidance behavior of the cat (study with Dr. Janice Stevens) and the monkey during hippocampal seizures induced by injection of crystalline carbachol into the hippocampus. Emphasis was placed on the prolonged catatonic-like stances following the excited, confused type of behavior in the test situation. The foregoing behavioral observations introduced the consideration of the effect of reserpine (Serpasil) and other drugs on the electroencephalogram. Work in progress with Dr. C. Kim indicates that administration of reserpine in the cat may result in almost continuous regular activity at 3 to 4 cycles per second in the hippocampus during periods when the neocortex shows desynchronized activity of the waking state. Low-voltage activity of the same frequency as that in the hippocampus may be recorded in the region of the hypothalamus. Studies with Drs. Flanigan and E. Gabrieli were described which suggest that metabolism of the hippocampus might be differentially altered by pharmacologic agents. Administration of S^{35}-labeled methione to the rat results in particularly high radioactivity in cells of the hippocampus. In general, the depths of contrast seen in radioautographs of brain resemble Nissl-stained sections. In summary, accumulated findings were enumerated that clearly distinguish physiology of the hippocampus from that of other cortical structures.

DISCUSSION

DR. RAYMOND D. ADAMS: I enjoyed hearing Dr. MacLean. He has been very kind in coming to Boston to keep us posted on his activities. There can be no doubt in the minds of any of us as to the importance of this part of the nervous system in the expression of emotion and its probable role in diseases for which we have not a very good pathophysiology. What is the difference between what you consider to be the stimulation effect, or continued functional effect of the limbic system, upon the animal and the paralytic effect? Also, your experiments would seem to indicate that there is some disturbance of awareness to environmental stimuli. How do you explain that phenomenon? Is there a loss of memory or capacity to acquire memory when the animal is in this stage as judged by your conditioning experiments? Or by any others?

DR. PAUL D. MACLEAN, Hamden, Conn.: When one stimulates a structure and time after time can elicit consistent motor responses, one never questions that one has obtained what Dr. Adams has referred to as a "stimulation effect." Such is generally the situation when one stimulates respective structures in the pyriform-amygdalar-hippocampal region, where one elicits a wide assortment of viscerosomatic and affective responses. The situation is far different when one stimulates in one of the so-called "silent" areas of the brain. Except for the meager responses that have been described, the greater part of the hippocampus outside the amygdalar region is remarkably "silent" when the stimulus intensity is below threshold for inducing a hippocampal seizure. If a propagating hippocampal seizure is induced, however, the seizure has a tendency to spread in and be largely confined to limbic structures, and quite dramatic changes in the animal's behavior can be demonstrated. The assumption is that when seizure activity is present in a structure, it is incapable of integrating and acting upon the impulses that would normally be flowing into it. It is for this reason that the statement was made that a propagating hippocampal seizure results in what must amount in part to a functional ablation of the limbic system. It might be expected that a large functional ablation, like a large surgical ablation, would reveal behavioral deficits that otherwise might not be detected. One might think of the cerebral cortex as a little like a mirror. One must fracture a large part of a mirror before it becomes useless, say, for shaving.

Dr. Adams' question about memory is a most difficult one. The animals shown during hippocampal seizures appeared as though they had retained some recollection for the significance of the conditioned stimulus. We have not yet performed experiments to ascertain whether or not an animal can acquire memory for events occurring during a hippocampal seizure. Dr. Kubie suggests that memory depends on the integration of internally and externally derived experience. I have elsewhere raised the question of whether or not the experiences of a patient during psychomotor seizures are lost to recollection because the limbic discharges interfere particularly with the recording of internally derived impressions.

DR. ROBERT S. SCHWAB: How long does it take for the hippocampal seizure to get to the other side?

DR. PAUL D. MACLEAN, Hamden, Conn.: An after-discharge induced in one hippocampus may be present for a variable time before spreading to the other hippocampus. Sometimes there seems to be an almost immediate spread; at other times, quite a latency. It is of interest that when respective limbic structures are activated by the local injection of cholinergic agents in solid form, the hippocampus may show almost continuous rhythmic activity at a frequency of around 4½ per second.

DR. PAUL I. YAKOVLEV: Have you done any ablation experiments on the hippocampus?

DR. PAUL D. MACLEAN, Hamden, Conn.: It is hard to do ablation of this area without getting into many other structures. Bard and Mountcastle have reported that bilateral ablations have resulted in enhanced pleasure reactions and increased placidity in cats—a finding that is particularly pertinent to this discussion in the light of the enhanced pleasure and grooming reactions we have seen when a drug-induced seizure of the hippocampus begins to abate or following a hippocampal after-discharge elicited by electrical stimulation. Rats, by the way, show very intensive grooming activity following hippocampal seizures, and occasionally there may be erections as they groom the region around the genitalia.

(Pribram has found in monkeys that bilateral ablations of the hippocampus result in rapid extinction of postoperatively acquired conditioned avoidance.)

Intra-Aneurysmal Hemodynamics. DR. WILLIAM J. GERMAN, New Haven, Conn., and DR. SAMUEL P. W. BLACK, Hartford, Conn.

A method has been developed for producing experimental "berry" aneurysms by grafting a vein-pouch upon an opening in the wall of the common carotid artery of dogs. As part of an investigation of stress-strain-time relations of aneurysmal rupture, the following factors have been studied: comparison of intra-aneurysmal and intra-arterial pressures, jet action, and turbulence.

The pressure within an aneurysm has the characteristics of side-pressure. Intra-aneurysmal pressure is very significantly increased by occlusion of the parent artery cephalad to the aneurysm and decreased by cardiac occlusion. Although all pressure elements are involved, the most marked changes are in pulse pressure. Intra-arterial pressure is slightly decreased cephalad to an aneurysm.

A jet of blood from a hole in the dome of an experimental aneurysm may attain a vertical height as great as 116 cm. and a calculated velocity as high as 477 cm. per second. The dynamic force of these free jets on the average is about 20% greater than the static-force equivalent of the pressure within the aneurysm.

Turbulence within an experimental aneurysm may produce a bruit. Cinefluoroscopic observations indicate the presence of vortex motion within the aneurysms, irregular swirling, and retention of opacification beyond that of the parent artery. There is a peculiar cross flow at the aneurysmal neck.

DISCUSSION

DR. RAYMOND D. ADAMS: Is there anything that would tell us why the proximal part of the neck is the soundest part of it? Why are there ischemia and degeneration of tissue distal to a ruptured aneurysm? Is the pressure distal to the aneurysm reduced long enough to cause an ischemic necrosis?

DR. JOSEPH J. FOLEY, Middleboro, Mass.: Are there any histological observations on the vessels after they have been sutured for a period of weeks or months, particularly when there are changes in the wall of the grafted vein?

DR. WILLIAM J. GERMAN, New Haven, Conn.: The problem in relation to the axis of flow remains unsolved. It seems that regardless of change of the angle of the aneurysm, as shown in the glass model as the clamps are taken off, the flow springs up to right angles to the parent vessel. Concerning the difference in hemodynamics when there is a branch nearby, we hope to put the pouches onto a communication between the two carotid arteries. This would simulate the anterior communicating artery, an odd situation where the two pulses meet. Concerning the question of ischemic necrosis distal to an aneurysm, I do not know that it can be answered from the data we have. There is a tendency to loss of pressure head distal to an aneurysm, due to the expansile nature of the lesion, and a tendency to turbulence, which decreases the pressure

head in proportion to the square of the velocity. I doubt whether they would be enough, because they operate with the aneurysm unruptured. Something else must happen at the site of the aneurysm. As to histological changes, the aneurysms tend to have thick walls and simulate arteries. We have quite a number of aneurysms which have been taken out; the older they get, the thicker the wall. Perhaps that is why the older aneurysms lose the tendency to absorb the thrust. As to the tendency to rupture at its dome, I do not know the explanation. A hydrodynamic fact is that, as the jet spurts into the neck, it is directed toward the dome. The force of the jet is maximal when obstructed or interfered with; the jet would therefore assert its maximum effect at the dome.

Erich Lindemann, M.D., *President, Presiding*

Regular Meeting, April 21, 1955

Cysticercosis Cerebri: A Diagnostic and Therapeutic Problem of Increasing Importance. DR. JAMES C. WHITE, DR. WILLIAM H. SWEET, and DR. EDWARD P. RICHARDSON JR.

The recent literature on infection of the human brain by the larval form of Taenia solium indicates that this condition is becoming a neurosurgical problem of increasing importance. This is true not only in countries with poor hygiene but also here and in England.

Cysticercus cellulosae in the brain gives rise to varied clinical manifestations, which may resemble brain tumor, pseudotumor (cerebral hydrops), Alzheimer's or Pick's disease, or syphilitic meningitis.

Three case histories are reported of patients with this condition seen in the Massachusetts General Hospital during the past two years. One had lived in this country for 36 years.

The first two cases represent the favorable type of solitary cyst, which resembles a brain tumor by production of localizing symptoms and signs. In each of these cases obstructive hydrocephalus was erroneously attributed to a midline tumor in the posterior fossa. Relief was obtained by removal of the obstructing cyst from the fourth ventricle. In the second case, complicating recurrent adhesions blocking the outflow of cerebrospinal fluid necessitated further surgery to reestablish ventricular drainage.

The third patient suffered from epileptic seizures due to multiple calcified cysts scattered through both hemispheres. No operation has been necessary, as the fits have been controlled by anticonvulsant medication.

Two other varieties of intracranial cysticercosis have been described. The first, with multiple intracranial cysts, often leads to fatal edema of the brain; the second, to serious hydrocephalus from the presence of racemose cysts blocking the basilar and ambient cisterns.

In order to diagnose and treat this disease effectively, it is necessary to know its common clinical forms, to realize its frequency in certain countries where hygiene is poor, and to bear in mind that the parasite may cause trouble many years after its entry into the blood stream.

Valuable diagnostic tests are eosinophilia of the blood and spinal fluid, a positive complement fixation by the cerebrospinal fluid to an alcoholic extract of porcine cysticerci, and roentgenographic techniques.

DISCUSSION

DR. DAVID GAMSU: Cysticercosis is quite prevalent in South Africa, particularly in the Bantu population. A number of cases were admitted to hospital because of epilepsy in which the diagnosis was obvious. These cases revealed scattered calcified areas easily visible in the brain, characteristic of cysticercosis. Frequently areas of calcification were too numerous to count. These patients were placed on anticonvulsant medication and were left alone unless something gross developed. Surgery is unjustifiable where only one focus is removed and hundreds of others are left. Follow-up is impossible in the Bantu population, for, once treatment is over, the patient returns to his tribe and is not seen again.

In regard to the question of Multiceps multiceps, I have seen four cases in the white population which presented collections of cysts in the form of grape-like clusters in the posterior fossa. The first three patients were operated upon and did fairly well at the time of operation, but later symptoms recurred. At autopsy multiple cysts were found in the subarachnoid space around the tentorium. The fourth, a man of 40, presented a posterior fossa lesion, with increasing headache, papilledema, vomiting, vague cerebellar signs, increased pressure, and increased protein. Investigation showed him to have hydrocephalus, with a obstructive lesion in the posterior fossa.

At operation grape-like cysts were found in the cisterna magna and fourth ventricle and were removed. A Torkildsen procedure was performed. The patient recovered and left after two weeks, apparently quite well. He returned in three months with recurrence of symptoms, but without the cerebellar signs. Pressure was 500 mm. The site of incision had started to yield. I opened the incision again but found no evidence of recurrence of the cysts. He had one large arachnoid cyst, with free connection between the fourth ventricle and the lateral ventricles, viz., a communicating hydrocephalus. The pathological lesion was therefore at the tentorial notch, interfering with the return of the cerebrospinal fluid. It was felt that an attempt to do an anterior third ventriculotomy would result in failure, as no drainage could be expected. I did an arachnoidoperitoneostomy, with a tube leading from the lumbar subarachnoid into the peritoneal space. He did well postoperatively; the pressure ramained at almost zero. When last seen, the patient was perfectly well. Apparently there is no systemic treatment to get rid of the cysts or to stop them from recurring.

DR. SOLOMON HAKIM: The paper of Dr. White, Dr. Sweet, and Dr. Richardson gives us a very good conception of the problem of cysticercosis of the brain. I should like to summarize some of the conclusions that Dr. Alejandro Jiménez and I arrived at in several cases we saw in Bogotá, Colombia. A report of our first four cases was published in 1954 (Cisticercosis del encefalo en Colombia, *Rev. Hosp. San Juan de Dios, Bogotá,* Vol. 2, No. 6, 1954). We have since examined and studied nine more cases. The importance of this disease in Boston, of course, is due not to its high incidence in this vicinity but, rather, to its occurrence in patients who come to this medical center for neurological and neurosurgical care. For this reason, it is perhaps worth while to be familiar with this troublesome disease.

Cysticercosis of the central nervous system should be regarded as a chronic, multifocal condition, especially when it is located in the parenchyma. The classifications that have already been proposed by Griesinger, Sato, Hanneberg and associates, Tyczka and Ran-Prussakowa, and, finally, Stephen and Chorobski are based mainly on the clinical symptoms and the location of the parasitic cysts, resulting in many groups, and thus become controversial and impractical.

A more practical and simpler classification is both desirable and possible. We preferred to divide our cases into three groups: (1) the intraparenchymatous group, in which the cysts were mainly located supratentorially; (2) cysticercosis of the cerebrospinal fluid pathway, which was primarily intratentorial, and (3) the mixed forms.

The reason for this grouping is that the parasitic implant can be either in the parenchyma or in the cerebrospinal fluid system or in both.

DR. ROBERT S. SCHWAB: Recently, when I was in Uruguay, I saw an exhibit of hydatid cysts in the brain with their EEG findings. The chief problem was that the large size of these space-occupying masses produced widespread electrical abnormality, which sometimes confused the localization considerably. There was some discussion of other types of cysts in this exhibit.

Personality Correlates of Two Phases of Stress Reactions. DR. D. H. FUNKENSTEIN, DR. S. H. KING, and MR. M. E. DROLETTE.

One hundred twenty-five healthy college students studied during laboratory stress experiments were scored on two aspects of their stress reactions: (1) their acute emergency reactions, in terms of the immediate emotion expressed by them, and (2) their ability to handle stress as time passed, in terms of mastery or failure in mastery of the stress.

Personality data were collected by psychiatric interviews, psychological tests, and sociological questionnaires. Certain personality data correlated with one aspect of stress reactions, and certain other personality data correlated with the other aspect of stress reactions.

The statistically significant personality correlates of the acute emergency reactions were (1) the subjects' perceptions of their parents, (2) their concept of self, (3) their fantasies, as determined by the Thematic Apperception Test, (4) their social attitudes, and (5) their social class.

The statistically significant personality correlates of the ability to handle stress as time passed were (1) measures of interpersonal relations, (2) the ability to assess reality, and (3) the integration of the personality.

The working hypotheses based on this work and on other work of ours are as follows: The acute emergency reactions represent one aspect of personality, namely structure, and are predictive of the emotional content of a psychosis or psychosomatic illness should one develop;

the ability to handle stress as time passes represents a different aspect of personality, namely function, and is closely related to the proneness to develop a psychosis or a psychosomatic illness.

DISCUSSION

DR. ERICH LINDEMANN: The authors are to be thanked for an overwhelming amount of data, brought together in a remarkably appealing way in their slides. Obviously, a great deal of work has been going on in the area of conceptual scheme and the correlations. It is a problem to pick out a point at which to start. I might ask a simple question. How did you motivate these young men to stick at it that long? How can you compare these students with psychotic patients, whose motivational set is so different?

DR. WILLIAM H. SWEET: I should like to know more about the test procedure.

DR. D. H. FUNKENSTEIN: The question concerning the method used to motivate the students was an extremely important one. Without adequate motivation there can be no stress experiments. We put a great deal of thought into this problem in planning the project. We represented to the subjects the authority of the college, especially since we had the cooperation of some college authorities in obtaining the subjects. In addition, we personally talked to every man prior to the start of the project, explaining its purpose. Fifteen minutes of each testing period was set aside for "passing the time of day" with the student in order to build a relationship. Again, the college newspaper was read so that if a student had won an honor he could be congratulated on it when he next came to a testing session. All of this contributed to the building of a positive relationship between the personnel working on the project and the subjects.

The psychotic patients have not been studied in a stressful situation. We imply that psychotic patients are under constant stress whose stimulus is within their own personalities. During stressful situations students will show emotional and phyiological reactions similar to those manifested by the psychotic patients during nonstressful situations. During nonstressful situations students do not show reactions similar to psychotic patients.

The method of inducing stress was by using an apparatus which we termed a "sonic confuser." The subject speaks into a microphone and hears his own voice 0.2 second later through a headset. Probably owing to interference with the "feedback" of the voice, stammering and other difficulties in speech are induced. Using the "sonic confuser," the student was asked to repeat a "culture-free" story from memory as rapidly as possible. This resulted in difficulty in speech and marked frustration, with an accompanying emotional reaction.

Recovery from a Brain Operation. DR. HANNIBAL HAMLIN, Providence, R. I.

The recuperative properties of the human brain are seldom brought to us by the thoughts and feelings of the patient himself. A case history is presented of a newsman who underwent a negative exploratory craniotomy under local anesthesia on suspicion of tumor of the left hemisphere. Being a converted left-hander, he developed transient aphasia and apraxia along with hallucinatory and depersonalization experiences.

During his convalescence he was persuaded to write about his reactions and attitudes during the acute recovery period, partly as a rehabilitation device and also in the expectation of extracting information of neuropsychologic interest from a person possessing unusual insight and expository ability. The literary product of his recall concerning the manifold difficulties of his early postoperative experience proved to be a cogent and witty revelation of the belabored notion that the dysphasic is intellectually aware of much more than the casual observer may realize.

DISCUSSION

DR. ERICH LINDEMANN: This story is one we rarely hear from a patient—the reactions of the patient's total personality to his defect, his frustration and feelings, and his way of feeling and experiencing what he calls hallucinations.

DR. WILLIAM H. SWEET: Dr. Hamlin and I were entranced by this man's capacity to analyze and express his feelings. We have had occasions since to guide ourselves and others in recoveries. Another patient had hallucinations: Although he weighed 200 lb., he felt he had diminished to the size of a Tom Thumb. He was terribly afraid that someone would throw him away with the laundry. Some people made fun of this. His resentment was extreme. Later on, when he had recovered and had lost his hallucinations, he still had resentment for people who

had not been sympathetic with him. The account given by Dr. Hamlin makes it clear what an interesting task we have, not only to appraise the unreal situation of the patient but also to help him through it.

DR. WILFRED BLOOMBERG: While it is true that this man was a very articulate patient, who could say how he felt, we should give credit to Dr. Hamlin for having asked him. Too often, we just don't ask, and don't listen. If there were more people like Dr. Hamlin among doctors, it might not have been necessary to invent the word "psychosomatic."

DR. ERICH LINDEMANN: From the point of view of investigative work with forms of sensory disturbance, especially with the whole area of hallucinations, there might be enormous opportunities with patients like this. One is reminded of the kind of sensory disturbance of patients under mescaline and lysergic acid. They also have a disturbance in the perception of size.

PHILADELPHIA PSYCHIATRIC SOCIETY

Manuel M. Pearson, M.D., Chairman

Regular Meeting, March 11, 1955

Clinical Hints from Dream Studies. DR. BERTRAM D. LEWIN, New York.

Hughlings Jackson's statement, "Find out all you can about dreams, and you will have found out all about insanity," has been supported by observations of Griesinger, and later amplified by Freud. Dreams fulfill the same infantile wishes as those encountered in the psychoses and neuroses, but, also, according to Freud, serve the purpose of preserving sleep. In the "Metapsychological Supplement" to the "Theory of Dreams," published in 1916, dreams are described as hallucinatory wish fulfilment psychoses, due to the wish to sleep. Sleep is not a simple physiological problem, but a manifestation of narcissism. The dream interferes with this regression; it is made up of remnants from waking life of various wishes and interests which, as it were, did not go to sleep with the rest of the person. Studies on dreams and hypnagogic states, paralleled with studies of symptoms, have shed some light on the sleep state itself, and also on the concept of narcissism in relation to sleep and the psychoses.

The ordinary dream is a visual projection, which implies some kind of a "screen" on which the images are projected. Some patients have described such "dream screens" as rolling up as they watched the action, just as a moving-picture screen or canvas would roll. These observations seem to be related to the phenomena reported by Isakower in the hypnagogic state, in which the beginning sleeper has a sudden hallucination of the approaching of large masses, which seem to grow larger and larger as they get nearer and finally merge with the sleeper to the accompaniment of skin and mouth sensations. The interpretation of these experiences as repetitions of the earliest nursing experiences of the child falling asleep at the breast may be expanded to consider the "dream screen" as the breast.

The consideration of blank dreams leads to a modification of this idea. Many blank and nearly blank dreams are not located in front of the dreamer; instead, dream and dreamer occupy the same segment of space and are not separated. Such a dream is reported by Rycroft: "It felt as though you [the analyst] had taken me under your wing. There was nothing to see in the dream at all. It was like a white sheet." In these dreams, there is marked emotional content with little or no visual imagery. The interest is centered on sleep itself, and the dreams thus form concrete examples of what Freud means by the narcissism of sleep.

If dream and psychosis are of the same order, it follows that going to sleep is a prototype of going into a psychosis, and, correspondingly, that waking-up fantasies, called hypnopompic, are related to those occurring in the recovery from a psychosis. Thus it is possible to correlate blank dreams theoretically, and in some instances clinically, with elated manic attacks. While it is theoretically possible that a connection exists, the relation of the blank ecstatic dream to depressions has not been demonstrated by experience.

The origin of the blank dream in earlier analytic thinking might have been considered to be a regression to intrauterine life, but a much more plausible theory is that it reflects a state of mind in very early postnatal life. That this early instinctual activity is characterized by a desire to eat is generally recognized; the studies in blank dreams suggest two other components, the wish to sleep and the wish to be eaten or to be reincorporated in the mother. The elements in this "oral triad"—the wish to eat, the wish to be eaten, and the wish to sleep—are relatively independent, as can be illustrated by case material.

Much more remains to be done in these clinical investigations, but the concept of the dream as a psychosis should be of practical help in understanding both the process of sleep and that of psychosis.

DISCUSSION

DR. ROBERT WAELDER: Dr. Lewin's work is of great value as a new approach to preverbal development. Freud never stated positively that sleep was a regression to intrauterine life. In Homer, sleep is described as coming like a blanket or veil, and similar expressions are found in other classic literature. This idea may be akin to the "dream screen."

DR. CATHERINE BACON: Sleep in the child is used for growth, in the adult for restoring lost vigor; in any case it represents a reunion with the mother. The dream screen or breast rolling up indicates the presence of guilt feeling. In a depression a dream of eating a fowl was related to the idea that success is achieved only by the death of something, and the guilt in this case could be traced to the thought that the patient had caused his father's death. Orgasm, which sometimes occurs with blank dreams, may represent not union, as commonly thought, but intense hostility.

DR. SPURGEON ENGLISH: Dr. Lewin's approach is interesting in that it is directly opposite that usually adopted. We know a good deal about psychosis and much less about dreams. To try to understand psychosis through dreams is a valuable procedure.

DR. BERTRAM D. LEWIN, New York: Anthropology is of less help in studies of symbolism than is archeology. The Isakower phenomenon was described in the year 1000 A. D. by an Arab physician as being related to epileptic auras. Symbolism is often difficult because of the confusion of words. For example, "breast" and "womb" are very similar in many languages and identical in some.

I hope this presentation will stimulate some of the audience to investigate for themselves. I believe their efforts to either prove or disprove the accuracy of our theoretical conclusions will add appreciably to knowledge of psychopathology.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

TISSUE PREFERENCES FOR FATTY ACID AND GLUCOSE OXIDATION. A. ALLEN, B. FRIEDMANN, and S. WEINHOUSE, J. Biol. Chem. **212**:921, 1955.

It has been held for some time that fatty acid catabolism occurred only in liver cells and that extrahepatic tissues were exclusively or principally utilizers of carbohydrate. More recent evidence suggests that nonhepatic tissues, including brain, can oxidize fatty acids. Allen, Friedmann, and Weinhouse find that liver, kidney, heart, and brain of rats oxidized added C^{14}-labeled fatty acids, both in the absence and in the presence of nonlabeled glucose. The presence of glucose did not lower the oxidation of the added fatty acid. The oxidation of endogenous palmitic acid of tissue lipids was likewise little affected by glucose. There seems to be a basal fatty acid catabolism occurring generally in tissues which is not suppressed by abundance of glucose.

PAGE, Cleveland.

THE QUANTITATIVE HISTOCHEMISTRY OF BRAIN: IV. LACTIC, MALIC, AND GLUTAMIC DEHYDROGENASES, J. L. STROMINGER and O. H. LOWRY, J. Biol. Chem. **213**:635, 1955.

The amount of lactic and malic dehydrogenase has been determined in six layers of cornu ammonis; four layers of cerebellum; four layers of striate cortex, supraoptic nucleus, hypothalamus, and optic nerve and tract; four layers of retina, and four additional myelinated fiber tracts and dorsal root ganglion cells. Glutamic dehydrogenase was determined in layers of the cornu ammonis.

Aldolase parallels the distribution of lactic and malic dehydrogenase in cornu ammonis. Nonmyelinated fiber and dendrite layers are especially rich, in contrast with the distribution of glutamic dehydrogenase. The latter is found chiefly in myelinated fibers and the molecular layer of cornu ammonis. Three types of fiber tracts may be distinguished on the basis of lactic and malic dehydrogenase activity.

Retinal ganglion cells and their axons are rich in lactic dehydrogenase and poor in the malic variety. Deep in the retina some structures have a high malic dehydrogenase content and a low lactic dehydrogenase content. Thus, the high glycolytic and respiratory rates in intact retina are possibly manifestations of different metabolic processes in different cells.

PAGE, Cleveland.

ELECTROCONVULSIVE THERAPY IN THE PRESENCE OF PHYSICAL DEFECTS. W. K. MCKNIGHT, R. BURBRIDGE, and P. GUTH, J. Nerv. & Ment. Dis. **119**:478, 1954.

Electroconvulsive therapy was administered approximately three times a week to 124 patients, ranging from 15 to 85 years of age. Approximately 23,520 treatments were given, and curare was used before each treatment. There were 23 patients 65 to 85 years of age. Ten patients with arteriosclerotic heart disease, 3 with coronary occlusion, and 2 with angina pectoris were treated. Patients with tuberculosis, asthma, bronchiectasis, and senile emphysema were treated without ill effect, but one patient with an acute respiratory disease died of bilateral lobar pneumonia, perhaps aggravated by the aspiration of infective material during the treatment. Treatment was also administered to patients with vertebral fractures, metastatic carcinoma to the ilium and acetabulum, poliomyelitis, multiple sclerosis, Parkinsonism, diabetes, thyrotoxicosis, inguinal hernia, pregnancy, and peptic ulcer, with no ill effect. One patient with arteriosclerotic heart disease died of coronary occlusion shortly after treatment. The results indicate that this therapy can be administered in the presence of physical disease, but risks of continued mental illness in the presence of physical illness must be balanced against the risks of electroconvulsive therapy.

BERLIN, New York.

CONCERNING THE NEURAL MECHANISM OF PARKINSONIAN TREMOR. E. JEFFERSON BROWDER and HARRY KAPLAN, J. Neurosurg. **11**:528, 1954.

Browder and Kaplan describe the effect of surgical occlusion of the anterior choroidal artery upon the tremor of Parkinsonism. Usually, the passive tremor of Parkinsonism occurs at the rate of 4 to 6 per second, as recorded by electromyography. They have surgically altered, in previous operations, the cortical motor mechanism and its subcortical projections, the anterior limb of the internal capsule, the ansa lenticularis, and the cerebral peduncle, all of which are concerned with an abnormal hypothetical pathway. The authors feel that a sublethal injury results in a slowing of their frequency of firing. Therefore, with surgical occlusions of the anterior choroidal artery, which supplies the amygdaloid nucleus, a small part of the uncus, the subthalamic area, and part of the globus pallidus, there resulted a reduction in the rate of tremor to approximately one-half of that which previously existed. It therefore seemed likely that the "controlling" mechanism was in the subthalamic zone. This result was obtained in two of the five patients who submitted to this operation. MANDEL, Philadelphia.

NERVOUS MECHANISMS AND DARK-ADAPTATION. G. B. ARDEN and R. A. WEALE, J. Physiol. **125**:417, 1954.

Dark adaptation curves were measured for two observers. The central fovea and extrafovea at 8 degrees were examined with white fields subtending at the eye angles of 2.7 and 15 minutes for the former, and 2.7 minutes and 7 degrees, for the latter.

The foveal and extrafoveal absolute thresholds of the fully dark-adapted eye as measured with the 2.7-minute field were found to be nearly the same.

A comparison of the extrafoveal thresholds measured with the 2.7-minute and 7-degree fields after dark adaptation lasting 8 and 20 minutes, respectively, revealed that the integrating power of the retina increased with time. This suggests that part of the adaptive process consists in a change in the size of the receptive field.

The experiments revealed two points of interest: First, when the "rod" portion of the dark adaptation curve is measured with small and large test fields in the retinal periphery, the rate of adaptation is found to increase with the size of the test field in the interval between 8 and 20 minutes after exposure of the eye to an adapting light. The simplest explanation of this finding is to assume that the size of the receptive field increases during dark adaptation. The other noteworthy point is that the difference in threshold as between foveal and extrafoveal regions, observed when both are tested with fields subtending at the eye angles of the order of 1 degree, is entirely due to spatial summation. When its effect is reduced by the use of test fields whose angular subtense is commensurate with that of each percipient element, foveal and extrafoveal thresholds of the dark-adapted eye are nearly equal.

These two findings provide independent support for the belief in a nerve component of dark adaptation. They invalidate the view that the introduction of various finesses into subjective measurements of dark adaptation curves—such as varying the duration, intensity, or continuity of the preliminary light adaptation—can yield any worth-while information as regards the dynamics of the photochemical processes underlying the visual act. THOMAS, Philadelphia.

PRODUCTION OF AFTER-BURSTS IN ISOLATED UNANAESTHETIZED CEREBRAL CORTEX. B. DELISLE BURNS, J. Physiol. **125**:427, 1954.

Repeated stimulation at a frequency of 0.1-5.0/sec. given to slabs of neurologically isolated cortex can produce a focus for periodic spreading after-bursts of neural activity which may persist for an hour after stimulation has stopped. These after-bursts do not all invariably originate from the stimulated area.

The stimulus strength necessary for the production of a series of after-bursts must usually exceed 1.5× threshold strength for the burst response to a single stimulus. The number of after-bursts produced by a period of conditioning stimulation is increased in linear fashion by increase of either stimulus strength of number of stimuli (where stimulus frequency and duration remain constant). When the number and strength of the conditioning stimuli are kept constant, more after-bursts are produced at 0.3/sec. than at any other frequency of stimulation.

A train of after-bursts can be permanently stopped by temporarily clamping the blood supply to the brain, although this procedure does not produce any lasting change in cerebral excitability.

Local current flow, passing radially inward through the gray matter, can produce a focus for spasmodic bursts of similar activity. Local, radially inward-directed current flow will also cause a continuous discharge of the cells conducting the burst response. Their discharge frequency increases linearly with increase of polarizing current. Local, radially outward-directed current flow can eliminate a focus for after-bursts.

After stimulation, a long-lasting radial potential gradient can sometimes be demonstrated beneath the stimulating electrodes such as to make the cortical surfaces some 200μv positive to points 1 mm. deep. The magnitude of this relatively persistent potential change is positively correlated with the frequency of after-bursts.

The experimental results have been interpreted as indicating that after activity, whether driven or spontaneous, the deep somatic ends of the neurones conducting the burst response repolarize more slowly than do the superficial ends. It is supposed that current flow between superficial and deep ends of these structures, during recovery from activity, is responsible for their subsequent spontaneous discharge.

THOMAS, Philadelphia.

Neuropathology

CEREBRAL VASOTHROMBOSIS IN CARDIAC DISEASES. I. M. SCHEINKER, Ann. Int. Med. **42**:128, 1955.

Cerebral vasothrombosis is characterized by thrombotic occlusion of distended and congested small cerebral veins. This condition occurs frequently in cases of chronic heart failure. Scheinker reports 15 cases. Gross examination of the brain at autopsy revealed numerous areas of hemorrhagic discoloration throughout both cerebral hemispheres. The leptomeninges showed brownish discoloration but no evidence of subarachnoid hemorrhage. The arteries had varying degrees of arteriosclerosis, but no occlusion could be demonstrated. Coronal sections revealed multiple areas of hemorrhagic softening in the gray matter. Microscopic examination revealed organized thrombi of varying areas in the small cerebral veins. There were disseminated areas of hemorrhagic infarction, involving the gray matter principally. The cortical capillaries were dilated, congested, and surrounded by perivascular hemorrhages. Glial reaction was minimal. The ganglion cell changes were similar to those observed in cerebral hypoxia. The subcortical white matter was characterized by an alveolar appearance. These findings were associated with arteriosclerotic and hypertensive heart disease, myocardial infarctions, and rheumatic heart disease.

Clinically, the cases were characterized by signs and symptoms indicative of diffuse brain disease and consisted of mental confusion, delirium, stupor, and delusions. Hemiplegia occurred in five cases. In 10 of the 15 cases there was clinical evidence of cardiac failure prior to the cerebral manifestations, and the patients' ages varied from 42 to 85 years.

MANDEL, Philadelphia.

Cholinesterases of the Central Nervous System. G. B. KOELLE, J. Neuropath. & Exper. Neurol. **14**:23 (Jan.) 1955.

Numerous investigations indicate that cholinergic transmission occurs at certain synapses in the central nervous system. The evidence for the theory that acetylcholine is a central neurohumoral transmitter is based upon findings similar or analogous to those obtained in earlier studies of the role of ACh in ganglionic and neuromuscular transmission. Koelle reports on a histochemical survey of the distribution of cholinesterases in the rat brain which was conducted to gain additional information concerning the presence and distribution of acetylcholine by inference. The cholinesterases comprise a group of enzymes which can be classified under two types: specific (true, acetyl, aceto) ChE and nonspecific (pseudo, butyro) ChE. Both groups were studied.

Intense staining was noted in neurons of four classes: (1) motoneurons, such as the anterior horn cells; (2) neurons giving rise to preganglionic autonomic fibers, including those in the lateral horns; (3) neurons of certain correlation centers, such as the caudate nucleus, and (4) certain tertiary afferent neurons, such as those in the lateral thalamic nucleus. In these neurons, enzymatic staining was most concentrated in the cell membrane and continued into the dendritic and axonal prolongations as far as they could be traced. This corresponds to that which Boell and Nachmansohn found in the squid.

Nonspecific cholinesterases are present in higher concentration in the white fiber tracts than in the gray matter. They are also found in the glia and blood vessels. Their function has not been established.

The cholinesterases have become of considerable practical importance since the introduction of the organophosphorus "nerve gases" and insecticides, the toxicity of which is due to their anticholinesterase activity.

SIEKERT, Rochester, Minn.

Oxidases and Peroxidases of the Central Nervous System. L. ROIZIN, J. Neuropath. & Exper. Neurol. **14**:47 (Jan.) 1955.

Roizin brings together and correlates some selected histochemical, anatomophysiologic, and histopathologic observations related to indophenol of cytochrome c oxidases and peroxidases in the central nervous system. He notes that the terminology of oxidases and peroxidases has been confusing and briefly reviews the early history and studies concerned with these enzymes.

Cytochrome c oxidase is a conjugated protein with an iron-containing prosthetic group which is believed to be identical with that of hemoglobin, and it is one of the most widely distributed oxidizing enzymes found in the cells of aerobic organisms. Peroxidases have the same role in the cellular metabolism as that of the indophenol oxidases with the exception that they use peroxide instead of oxygen. Some of the biochemical properties are discussed, as well as several technical procedures for the determinations of the activity of indophenol (or cytochrome c) oxidases and peroxidases, about which there is no complete agreement as to the specificity of the reactions. Many investigators have studied the normal distribution of indophenol oxidases in the central nervous system, and it appears that enzymatic activity is very marked in the gray matter and negligible in the white matter, although a good deal of variation was found. Some investigators have attempted to analyze the structural and enzymatic changes which occur in developing nerve cells when they change from the passive to the active functional state. Some have observed that in guinea pigs, before the 41st day of gestation, the Nissl substance was absent; about the 41st day it appeared for the first time, and rapidly accumulated thereafter. In the same period of time there was a sudden rise in the activity of the cytochrome c oxidase. Others have observed that electrical activity can first be recorded from the fetal guinea pig at about the 46th day of gestation. It appears also that the quantity of oxidase in a tissue is proportional to its function or metabolic activity, and the oxidase potency of a tissue seems to depend on the power of the tissue for sustained function. Additional investigations disclosed a more or less direct relationship between the activity of indophenol oxidases and the vascularization in the central nervous system. Certain comments concerning these enzymes in histopathologic and histochemical correlation are reviewed.

SIEKERT, Rochester, Minn.

Psychiatry and Psychopathology

PSYCHOSIS DUE TO AMPHETAMINE. M. HERMAN and S. H. NAGLER, J. Nerv. & Ment. Dis. **120**:268, 1954.

Seven men and one woman developed toxic psychotic reactions following the ingestion of amphetamine. All of the eight had some previous behavior disorder, evident in antisocial behavior and indulgence in narcotic drugs or excessive amounts of alcohol. Three patients had taken a single 250 mg. dose, but the others had taken the 250-500 mg/day from the contents of Benzedrine inhalers for from three days to one year. The psychotic symptomatology consisted of excitement, fear, paranoid delusions, and auditory and visual hallucinations. Two subjects remained psychotic, but in the others recovery occurred in 1 to 32 days.

BERLIN, New York.

Meninges and Blood Vessels

RUPTURE OF AN INTRACRANIAL ANEURYSM DURING CEREBRAL ANGIOGRAPHY. KENNETH G. JAMIESON, J. Neurosurg. **11**:625, 1954.

Jamieson describes the case of a 39-year-old man who had a subarachnoid hemorrhage and was submitted to carotid angiography one week after the episode. An aneurysm of the left middle cerebral artery was demonstrated, but its exact site of origin was not noted. Since surgical ligation was thought to be the treatment of choice, he had a left carotid angiogram

repeated one week later with iodopyracet (Uriodone). However, the aneurysm ruptured after the injection, and it was noted on the x-ray films. Surgery was then attempted, but a large intracerebral hematoma was encountered and the patient died.

The author maintains that early angiography in subarachnoid hemorrhage offers much information and considerably outweighs the risk of rupture, which is remote. This was the only fatality in 150 patients over a three-year period. The need for a new nonirritant dye in angiography is also discussed.

MANDEL, Philadelphia.

ANEURYSMS OF THE MIDDLE CEREBRAL ARTERY: REPORT OF SEVEN OPERATIVE CASES AND EVALUATION OF SURGICAL THERAPY. DANIEL PETIT-DUTAILLIS and HAL W. PITTMAN, J. Neurosurg. **12**:1, 1955.

Middle cerebral artery aneurysms constitute approximately 30% of all intracranial aneurysms; and of the patients with this type entering the hospital for subarachnoid hemorrhage, about 50% will survive without surgical treatment, 25% will be disabled, and 25% will succumb because of recurrent hemorrhage.

The authors report seven cases of middle cerebral aneurysms which were obliterated by clips or silk sutures, with recovery in five. They believe that intracranial clipping is the procedure of choice for middle cerebral aneurysm, since the artery is easily accessible and the mortality is low. In addition, any neurological disability which persists after clipping of the aneurysm is rarely greater than that prior to this procedure. There was no rupture of clipped aneurysms in this series or in any of the 76 cases reviewed in the literature. In contrast to this, patients in other series of cases who were subjected to cervical carotid ligation had an increased mortality rate because of subsequent rupture of the aneurysm. Two patients with ruptured cerebral aneurysms had only surgical evacuation of the clot and died. The procedure of choice for middle cerebral aneurysms appears to be intracranial obliteration of the aneurysm whenever possible.

MANDEL, Philadelphia.

FATAL SUBARACHNOID HEMORRHAGES IN PREGNANT WOMEN WITH INTRACRANIAL AND INTRAMEDULLARY VASCULAR MALFORMATIONS. ERNA CHRISTENSEN and HELGA LARSEN, Acta psychiat. et neurol. scandinav. **29**:441, 1954.

The authors present five cases of subarachnoid hemorrhage complicating pregnancy. It is well known that the blood volume, rate of blood flow, and minute volume increase during the first nine months of pregnancy and drop in the period prior to delivery. The circulation appears to be in its greatest period of stress three to seven weeks prior to delivery.

Four of the five patients died during this period as a result of subarachnoid hemorrhage secondary to intracranial malformations. One patient had aneurysm of the circle of Willis (anterior cerebral); another had an arteriovenous aneurysm and angioma, and a third had an angioma of the cervical cord. The fourth patient had an asymptomatic chromophobe adenoma of the pituitary gland with subarachnoid hemorrhage. No associated aneurysm was found in the last case. The fifth patient had a spontaneous subarachnoid hemorrhage during the ninth month of pregnancy and subsequently delivered a normal child and remained asymptomatic.

The danger of subarachnoid hemorrhage during pregnancy is emphasized, particularly if malformations such as aneurysm are present.

MANDEL, Philadelphia.

Diseases of the Brain

CALCIFIED INTRACRANIAL TUBERCULOMA. R. MUDD, I. PERLMUTTER, and R. E. STRAIN, Am. J. Roentgenol. **73**:19, 1955.

Mudd, Perlmutter, and Strain report the case of a Negro boy who was 9 years of age when he had onset of headache, vomiting, stiff neck, and lethargy, about a week after an illness diagnosed as measles. The clinical diagnosis at that time was measles encephalitis. He was seen three and one-half years later because he was having convulsive seizures, affecting chiefly the right side of his face and the right upper and lower extremities. At this time he had headache, mental confusion, and difficulty in walking. Lumbar puncture revealed normal spinal fluid pressure; 160 cells per cubic millimeter, with 88% mononuclears, and 484 mg. of protein, 33 mg. of sugar, and 670 mg. of chlorides per 100 cc. The Mantoux intradermal test for tuberculosis

was negative. Roentgenograms of the skull revealed a calcified density located deep in the left posterior fossa. The coronal sutures were separated, and there was thinning of the left occipital bone in the region of the calcification. Roentgenograms of the chest were normal.

A left suboccipital craniectomy was performed, and a large cystic and solid tumor was found to occupy almost the entire left posterior fossa. It extended superiorly through the incisura into the middle fossa and inferiorly through the foramen magnum, where it was adherent to the medulla. The patient died two days after operation of bilateral pneumonia, spontaneous perforation of the esophagus, and mediastinitis.

Tuberculomas constitute approximately 2% of brain tumors, but only about 5% of intracranial tuberculomas show calcification. Tuberculomas are most frequently located in the cortex of the cerebrum and cerebellum, probably because of the greater vascularity of these sites.

WEILAND, Grove City, Pa.

INFECTIOUS MONONUCLEOSIS ENCEPHALITIS. CHARLES R. REAM and JOHN W. HESSING, Ann. Int. Med. **41**:1231, 1954.

Ream and Hessing report a case of infectious mononucleosis which was complicated by encephalitis. The patient, a 22-year-old white woman, had the typical clinical and hematological picture of this disease and, in addition, presented evidence of psychotic manifestations. These symptoms were present at the onset of the disease, as well as aphasia, which cleared when the patient improved clinically. The spinal fluid serology was negative. The spinal fluid heterophile agglutination was negative, but there was a pleocytosis of the spinal fluid with an increase in protein. An electroencephalogram was not done during the acute phase of the illness, but on the 14th day it was found to be diffusely abnormal. The patient recovered completely and had no ill effects. Encephalitis occurs as a complication of infectious mononucleosis in 0.7% of cases.

MANDEL, Philadelphia.

A MORPHOLOGICAL CRITIQUE OF TEMPORAL LOBECTOMY. L. CROME, Lancet **1**:882 (April 23) 1955.

Crome takes issue with the significance of reported lesions found on biopsy after a temporal lobectomy which are alleged by various workers to account for most cases of "temporal lobe" epilepsy. From his studies he concludes that such diffuse and microscopic abnormalities occur in the temporal lobes of patients with no such clinical picture; moreover, their detection is unreliable. His study, based on the examination of pathological material obtained from the brains of mentally defective children with epilepsy, revealed that the brain lesions were neither peculiar to nor confined to the temporal lobe. His material further suggests that in "temporal lobe" epilepsy lesions when present in one temporal lobe will be accompanied by others elsewhere in the brain in many cases. He believes that the microscopic appearances forming the sole abnormality in most of the published cases are not peculiar to "temporal lobe" epilepsy. He questions whether the presence of certain lesions in the temporal lobes proves their relationship to epilepsy or other symptoms. He emphasizes that further investigation is necessary before importance is attached to microscopic findings which have been alleged to be responsible for "temporal lobe" epilepsy in many of the published cases of temporal lobectomy.

YASKIN, Camden, N. J.

Diseases of the Spinal Cord

SPINAL CORD INJURIES: A REVIEW OF THE EARLY TREATMENT IN 300 CONSECUTIVE CASES DURING THE KOREAN CONFLICT. GORDON T. WANAMAKER, J. Neurosurg. **11**:517, 1954.

The author presents a series of 300 consecutive cases of spinal cord injuries admitted to Tokyo Army Hospital from September, 1950, to May, 1952, and discusses the mortality resulting from the methods of early treatment.

The aim of the treatment during the early phase of paraplegic care was to salvage as much neurological function as possible and to prevent the formation of decubitus ulcers and other complications that would retard a rehabilitation program. The patients in this series received the same treatment as was advocated by neurosurgeons at the end of World War II. Laminectomies were performed on all patients with penetrating wounds of the spine, as well as in all cases of closed spinal cord injuries with fracture or dislocation of the spine. Decubitus ulcers

were prevented by turning the patient every two hours by means of the Stryker frame or by the double-litter method. One hundred ten suprapubic cystostomies were done. Body casts were not used because of the inability to care for the skin and inability to regulate body temperature. Patients with thoracic or lumbar injuries were given back braces and were allowed to sit up by the 10th postoperative day. Whole blood was given when indicated but no blood substitute such as plasma. Antibiotics were given in cases of infection.

Cervical cord injuries accounted for 18% of the cases. Four of the seven cases who had acute closed cervical cord injuries were treated by laminectomy and showed improvement. This type of treatment has not been approved by many authorities. The patients with penetrating wounds of the cervical spine showed a better result, with 13 out of 20 improving.

Thoracic injuries were responsible for 42% of the cases and were frequently associated with concomitant lesions in the thoracic and abdominal cavities, necessitating a delay in laminectomy.

Only 6 (23%) of the patients who suffered lumbar cord and conus injuries improved after surgery.

However, in the cauda equina injuries, 52% of the patients showed improvement following surgery. The over-all mortality in this series was 1%. MANDEL, Philadelphia.

SYNDROME OF HERNIATION OF THE LOWER THORACIC INTERVERTEBRAL DISCS WITH NERVE ROOT AND SPINAL CORD COMPRESSION. JOSEPH A. EPSTEIN, J. Neurosurg. **11**:525, 1954.

Epstein describes four cases of herniated thoracic disc in patients who had presenting complaints of abdominal and back pain. In two of the cases the pain resembled that of gall bladder or renal colic, and in the latter case the uterus was unsuccessfully removed in an effort to relieve the pain. The diagnosis was established by careful neurological examination and myelography. All patients benefited by removal of the degenerated disc tissue.

The author reviews the current literature on herniated thoracic discs and states that heretofore the syndrome has been regarded as rare compared with lumbar and cervical herniation; nevertheless, the frequency of disc degeneration with ridge formation and actual herniation at the 11th thoracic interspace is significant and deserves emphasis.

Clinically, the syndrome occurs in middle and late adult life, the average being 50 years, and affects women more frequently than men. The history of radicular pain is present in 50% of the cases, and since the lower thoracic spine is involved most frequently, the pain radiates to the abdomen and groin, thereby simulating disease of the abdominal viscera, especially the kidney. Angina, pleurodynia, and intercostal neuralgia are simulated by upper thoracic herniated discs. Sensory disturbances consist of hypersensitivity of the skin or partial numbness. Midline protrusions are insidious and painless and are manifested by signs of spinal cord compression, which include spasticity and ataxia caused by interference with the pyramidal and spinocerebellar pathways. A Brown-Séquard sensory defect may be present in these cases.

Laboratory studies, including spinal tap with manometrics, may be of value in disclosing a subarachnoid block, but the spinal fluid pressure is frequently normal in early cases. Myelography with fluoroscopy is of greatest value in establishing a preoperative diagnosis.

The treatment is surgical, and prognosis is hopeful if the diagnosis is established early, when minimal cord compression and radicular compression exist. MANDEL, Philadelphia.

THE SYNDROME OF ACUTE CENTRAL CERVICAL SPINAL CORD INJURY. RICHARD C. SCHNEIDER, GLENN CHERRY, and HENRY PANTEK, J. Neurosurg. **11**:546, 1954.

The authors describe nine cases of acute cervical spinal cord injuries which suggested a syndrome characterized by disproportionately more motor impairment of the upper than of the lower extremities, bladder dysfunction, and varying degrees of sensory loss below the level of the lesion. If the findings are caused by hematomyelia, there may be caudad or cephalad extension of the lesion with progression of symptoms, culminating in quadriplegia or death. However, if the symptoms are caused by concussion or contusion, an edematous type of central cord involvement occurs, and there will be a gradual return of function in a definite sequence. The amount of recovery depends on the degree of edema present as compared with the extent of hematomyelia. The lower extremities recover motor power first, with bladder function next and finally strength in the upper extremities.

The syndrome of acute central cervical spinal cord injury occurs most frequently in severe hyperextension injuries which cause a simultaneous squeezing or pinching of the spinal cord anteriorly and posteriorly. This may occur without apparent damage to the bony spine, having been caused by an inward bulge of the ligamentum flavum during hyperextension. Such injury may be suspected when a patient shows lacerations or contusions of the face or gives a history of having fallen forward on his face. The syndrome may also be found in compression fractures or cervical arthritis.

The authors state that recognition of this syndrome is important, for it may imply a good prognosis and surgical decompression is contraindicated. Surgery has been shown to harm these patients, rather than benefit them.

MANDEL, Philadelphia.

SPINAL CORD TUMOR IN A NEWBORN. DWIGHT PARKINSON, HARRY MEDOVY, and J. R. MITCHELL, J. Neurosurg. **11**:629, 1954.

The authors report a case of a spinal cord tumor in a newborn infant which was detected at birth, when neurological examination revealed a sensory level at T 11. Surgery was performed after myelography revealed a complete block at T 8, and a malignant glioma, possibly a neuroepithelioma, was completely removed. The child has shown improvement postoperatively.

Spinal cord tumors are rare in childhood, particularly in infancy. The authors have been unable to find any recorded case of a spinal cord tumor, other than teratoma and dermoid, which was evident at birth.

MANDEL, Philadelphia.

Peripheral and Cranial Nerves

COMPRESSION OF THE ULNAR NERVE AT THE WRIST BY A GANGLION. B. L. MALLETT and K. J. ZILKHA, Lancet **1**:890 (April 30) 1955.

Mallett and Zilkha report that a ganglion in front of the wrist joint may cause paralysis of the hand by compression of the ulnar nerve, either its main trunk, before bifurcation, or its deep motor division. Clinically, paralysis may be present in one of three ways: (1) paralysis of all the small muscles of the hand of ulnar innervation, with sensory loss in the ulnar territory; (2) a similar paralysis with no sensory loss, and (3) paralysis with no sensory loss and with sparing of the hypothenar muscles. They report two cases which represent the second group. Both patients were men more than 40 years of age; in both the onset was gradual and there was a history of trauma—in Case 1, a chronic occupational trauma; in Case 2, repeated sudden unusual strain of the wrist joint—and in both radiography showed osteoarthritis. In neither case was there any sensory loss, although at operation a ganglion was found compressing the main trunk of the ulnar nerve. After removal of the ganglion, improvement was considerable in the first case and slight in the second.

YASKIN, Camden, N. J.

Treatment, Neurosurgery

SIMPLICITY IN THE TREATMENT OF MENINGITIS. ARCHIBALD L. HOYNE, Ann. Int. Med. **41**:1164, 1954.

Hoyne reviews the therapy of meningitis from a historical standpoint and advocates the use of simple measures in the management of all cases of meningitis. He believes that a lumbar puncture should be reserved for diagnostic purposes only; more than one lumbar puncture is unnecessary in cases of purulent meningitis. However, if there is difficulty in isolating the organism or in establishing a diagnosis, more than one lumbar puncture is justified. If the patient has a positive blood culture or petechiae in the skin, lumbar puncture is not necessary. Repeated lumbar punctures are unnecessary in following a patient's clinical course.

In regard to intrathecal medication, the author feels that the estimated spinal level is about 50% to 75% of the blood level. Therefore medication can be administered orally, intramuscularly, or intravenously for satisfactory spinal fluid concentrations.

By using these principles as a basis, several thousand patients were successfully treated in the Cook County Contagious Disease Hospital. The fatality rate was 10% in cases of Meningococcus meningitis, 16% in Hemophilus influenzae meningitis, and 45% in tuberculous meningitis. None of the patients with tuberculous meningitis received intrathecal medication.

MANDEL, Philadelphia.

TREATMENT OF SPASTIC PARAPLEGIA BY SELECTIVE SPINAL CORDECTOMY. COLLIN S. MACCARTY, J. Neurosurg. **11**:539, 1954.

MacCarty reports four cases of paraplegia which occurred after traumatic injuries to the spinal cord and discusses the use of selective removal of spinal cord segments in order to reduce spasticity. This type of operation was first performed by the author in February, 1948, in an effort to eradicate a highly malignant glioma of the spinal cord.

Selective chordectomy was performed in these four traumatic cases as another method of producing flaccidity of the lower extremities to supplement the care of patients with spastic paraplegia. This method is compared to the removal of an atrophic cerebral hemisphere in patients suffering from infantile hemiplegia and uncontrolled convulsive seizures. The most striking effect of spinal cord removal is catabolic in nature, with manifestations of hypoproteinemia, decreased metabolic rate, and demasculinization. Spinal chordectomy below the cervical level produces flaccidity of the bladder. In high thoracic cord injuries, the author suggests that an isolated segment of cord be left in place in order to maintain reflex abdominal tone, in the hope of improving urinary bladder evacuation. In low thoracic cord injuries, the lumbar and sacral portions of the cord can be accurately removed.

MANDEL, Philadelphia.

TREATMENT OF TEMPORAL-LOBE EPILEPSY BY TEMPORAL LOBECTOMY. M. A. FALCONER, D. HILL, A. MEYER, W. MITCHELL, and D. A. POND, Lancet **1**:827 (April 23) 1955.

Falconer and his colleagues report that of 30 patients with intractable temporal lobe epilepsy submitted to temporal lobectomy, 12 became fit-free and 14 others were greatly improved as regards their epilepsy. A striking result in the series reported was that 20 were benefited in regard to their personality changes, 17 markedly so. The authors believe that the frequency with which improvement took place postoperatively in their cases was greater than that in most other series. The reason for this result was due to their policy of including the uncus and the cornu ammonis (and more recently the amygdala as well) in the tissue excised. They found pathologic changes in the regions mentioned above; 5 of the small macroscopic lesions involved those regions, in addition to the 12 cases of sclerosis of the cornu ammonis. For the past five years their criteria for operation in epileptics with temporal lobe seizures has been the presence of a unilateral EEG focus or bilateral foci in which one side is predominant. They conclude that good results are to be expected in any case of psychomotor epilepsy in which the focus is confined to one temporal lobe and major convulsive seizures have been absent or infrequent. The prognosis for surgery worsens when grand mal becomes frequent or the focus becomes bilateral.

In nine other cases a small macroscopic lesion was found (cerebral tumor, three; hemangioma calcificans, two; angioma, two; infarct, one; cicatrix, one). In the remaining 21 cases the lesions were microscopic and less circumscribed. In all the cases the nonspecific changes of meningeal fibrosis, focal or diffuse cortical atrophy, marginal gliosis, and gliosis of the white matter were present in various proportions.

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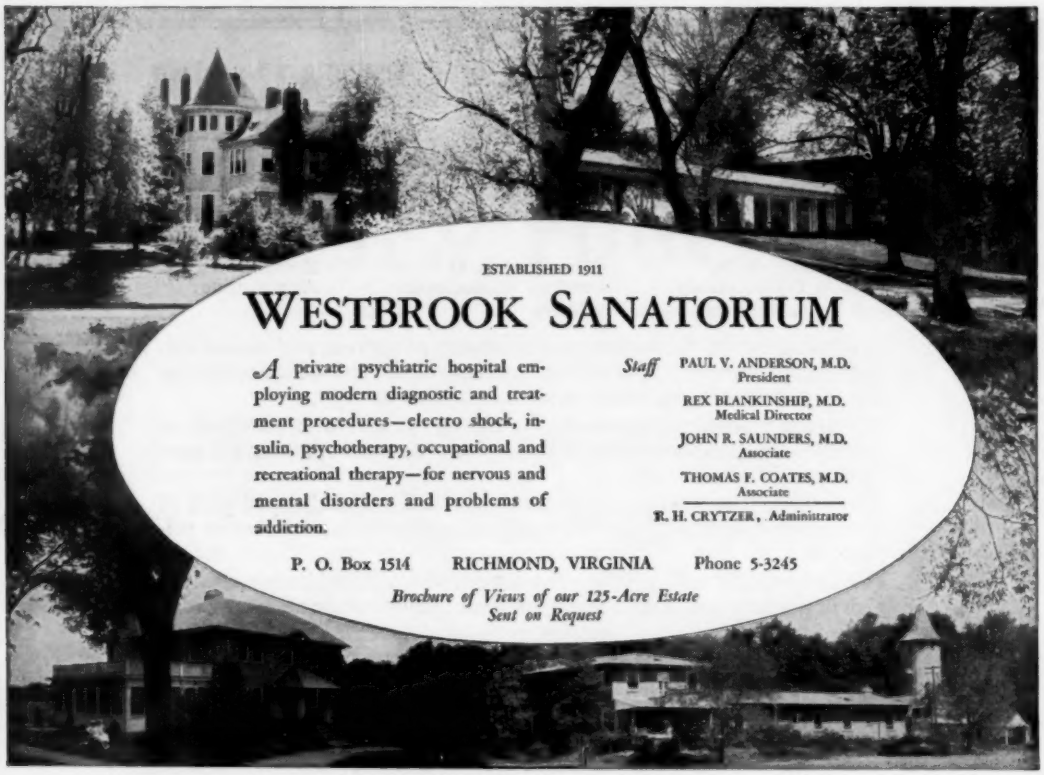
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